

The Chemistry
of Open-Chain
Organic Nitrogen
Compounds | *volume II*

*Derivatives of Oxidized Nitrogen:
Hydrazines to Nitrates*

PETER A. S. SMITH, *University of Michigan*

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The Chemistry of Open-Chain Organic Nitrogen Compounds: Volume II

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For One Who Is Dearest
and Others Who Are Very Dear

Preface

The organic chemistry of nitrogen has been an active exciting field at frequently recurring periods since Wöhler's synthesis of urea from ammonium cyanate and A. W. Hofmann's classic investigations of amines. Though both are now more than a century old, interest and excitement has not diminished. Nevertheless, few books have been devoted solely to this subject. One of the few, however, stands out clearly from the others: the delightfully written work by Neville Vincent Sidgwick, first published approximately forty years ago, in which countless chemists have found valuable help. It is now, unfortunately, long out of date, and its author is no longer with us, but all who write on the subject now and for some time to come are in his debt.

The purpose of my book is to give an interpretive as well as descriptive survey of the chemical behavior of functional groups containing nitrogen. The enormous field of heterocyclic compounds is excluded, in part because of its size and in part because it is adequately treated elsewhere. Polyfunctional and multifunctional compounds, such as amino acids, nitro alcohols, etc., have been largely ignored in order to keep the subject to manageable size. I have compiled the material for this book selectively rather than encyclopedically; although specific compounds and examples of a given reaction are severely limited, I have tried to be more comprehensive with respect to the kinds of reaction that each functional group has been observed to undergo.

The emphasis of this book is on reactions, with a moderate amount of information on mechanism when it seems that it might be helpful, whereas synthesis is assigned a secondary role. This is not really as arbitrary as it may seem, for most preparative methods for one type of organic nitrogen compound involve the reactions of another. In cases where this is not so, I have given a more extended treatment to the preparative reaction than otherwise. The references given in the sections on preparative methods have been primarily chosen to lead the reader to sources that are outspokenly devoted to synthesis, such as *Organic Syntheses*, *Organic Reactions*, and Houben-Weyl, as well as to appropriate journal articles.

I have chosen the references from a frugal utilitarian viewpoint, restricting them largely to those I thought would be most useful, in order to avoid suffocating the reader (and myself) in the vast morass of literature in the field. Reviews, summarizing articles, and leading references have been given preference over those representing earliest reports, and readily accessible sources have been strongly favored. All of this has meant that the publications (but I hope not the chemistry) written in languages other than English, German, and French appear infrequently among the references, and that the discoverer or major developer of a reaction may not necessarily have his articles referred to directly. No slight is intended, and I have tried to make sure that the omitted references could be found easily in the sources actually cited. Another consequence is that the bibliography is heavily biased in favor of recent publications.

The writing was completed early in 1965. Some references up to the last moment are included, but some contributions that should have been included have undoubtedly been overlooked, especially in the most recent period, and probably from earlier periods as well. If this book is helpful, however, it will have served its intended task.

It is a pleasure to acknowledge the hospitality of Professor H. Bredereck and the Institut für Organische Chemie in Stuttgart, which gave me the opportunity to begin the writing and bring it substantially forward during a sabbatical leave granted by the University of Michigan. The tolerant understanding of my family has allowed it to be completed; I thank them for so cheerfully putting up with both its primary and secondary domestic effects.

The willingness of my colleagues, students, and other friends in the chemical world to answer questions, engage in discussions, and to read and criticize portions of the manuscript from a lone paragraph to whole chapters has given me not only material aid, but much-appreciated moral encouragement. I thank them all most gratefully. Finally, the painstaking criticism of Professor Nathan Kornblum on virtually all details, from the major to the very minor, has allowed me to bring this book to a state of accuracy and clarity that I could not have achieved alone; it is a pleasure to record my thanks and appreciation for his wonderful help.

PETER A. S. SMITH

Ann Arbor, Michigan
September 1965

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ALKYL AND ARYL HYDROXYLAMINES

NOMENCLATURE

Hydroxylamines are best named as N-alkyl (or aryl) hydroxylamines when substituted on nitrogen, or as alkoxy (or aryloxy) amines when substituted on oxygen, although it is perfectly correct to use the form "O-alkyl (or O-aryl) hydroxylamine" when clarity is thus better served in the context of a discussion. Thus CH_3NHOH is N-methylhydroxylamine, NH_2OCH_3 is methoxyamine (or O-methylhydroxylamine), and $\text{CH}_3\text{ONH}\phi$ is N-methoxyaniline (or O-methyl-N-phenylhydroxylamine). When the presence of other functions makes it desirable to put the hydroxylamine function in a prefix, the forms hydroxylamino for $\text{HONH}-$ and aminoöxy for $\text{NH}_2\text{O}-$ are recommended; e.g., aminoöxyacetic acid, $\text{H}_2\text{NOCH}_2\text{COOH}$.

The older literature used the locants α - instead of O-, and β - instead of N-, and indeed, *Chemical Abstracts* used this system in its indexes until 1931. The death of these unsatisfactory symbols is agonizingly slow, however, and one still finds them used occasionally in publications outside the domain of fundamental organic chemistry.

The ions HONH_3^+ and NH_2O^- are called hydroxylammonium and aminoöxide, respectively, and their alkyl and aryl derivatives are named accordingly.

Sulfur analogs of hydroxylamine are best named as hydrosulfamines (rather than "thiohydroxylamines"). *Chemical Abstracts* lists them by this name only when the sulfur is not substituted, otherwise listing them as sulfenamides, after the sulfenic acids, RSOH .

PROPERTIES

The smaller alkyl hydroxylamines are volatile substances, liquids or low-melting solids, having a fishy, amine-like odor. O-Substituted derivatives boil lower than the N-substituted derivative, an expected consequence of the destruction of hydrogen bonding by the hydroxyl group, and methyl substitution at either position and to any extent results in increased volatility. The smaller alkyl hydroxylamines are very soluble in water.

All alkyl and monoaryl hydroxylamines are basic enough to form salts with mineral acids in the presence of water. Alkylation, with the possible exception of the first substitution on N, decreases the basic

strength, and O-substituted compounds are distinctly weaker than their N-substituted isomers.¹ This phenomenon was at one time attributed to prevention of tautomerism to an amine oxide structure when the oxygen is alkylated, but the explanation appears more likely to be concerned with solvation effects (see Chapter 2). Tetrasubstituted hydroxyl-

ammonium hydroxides, $R_3NOR^+ OH^-$, are strong bases, analogous to quaternary ammonium hydroxides.² Hydrosulfamines (sulfenamides) are evidently very weak bases, since they are not extracted from ether solution by dilute sulfuric acid.

Hydroxylamines have a weak acidity, undoubtedly resident in the hydroxyl group. The acid strengths have not been measured, and, indeed, would be difficult to measure, owing to the instability of most hydroxylamines in strongly alkaline solutions, but they are probably close in order of magnitude to hydroxylamine itself (pK_a est. 12–13; see Chapter 1), since the effect of substituents would have to be transmitted through the N—O single bond. Alkali metal salts have been prepared in anhydrous media,² and phenylhydroxylamine is reported to be markedly more soluble in aqueous alkali than in water (Table 8-1).

Most hydroxylamines are of only limited stability as the free base, particularly in the presence of air, but their salts with mineral acids are for the most part indefinitely stable.

The structure of methoxyamine has been investigated by electron diffraction,^{4a, b} which gives the value 1.43 Å for the N—O distance, shorter than the N—N distance in hydrazines and the N—C distance in alkylamines; the C—O—N angle is $111^\circ \pm 3^\circ$. Since a value of 1.45 Å has been determined^{4c} for the N—O distance in crystalline hydroxylamine hydrochloride and hydrobromide, it appears that the phenomenon of

Table 8-1 *Properties of some hydroxylamines*

Structure	mp	bp	pK_a of cation
H_2NOH	33°	$125^\circ*$	5.97
CH_3NHOH	38.5°	115°	5.96
$(CH_3)_2NOH$	17.6°	100.6°	5.2
CH_3ONH_2	-86.4°	48.1°	4.2
CH_3ONHCH_3	-97°	42.3°	4.75
$CH_3ON(CH_3)_2$	-97.2°	30.0°	3.65
<i>t</i> -Bu ₂ NOH	$65-66^\circ$	sublimes	
<i>t</i> -Bu ₂ NO— <i>t</i> -Bu		$85^\circ/11\text{ mm.}$	
$\phi NHOH$	82°		3.2
ϕ_2NOH	60°		
ϕONH_2		$72^\circ/7\text{ mm.}$	

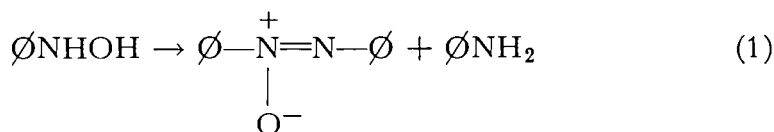
* Extrapolated value; bp 58° at 22 mm.

bond shortening exhibited by hydrazine between its free base and its salts does not occur with hydroxylamine.

The infrared spectra of the five methylated hydroxylamines have been analyzed in detail.⁵

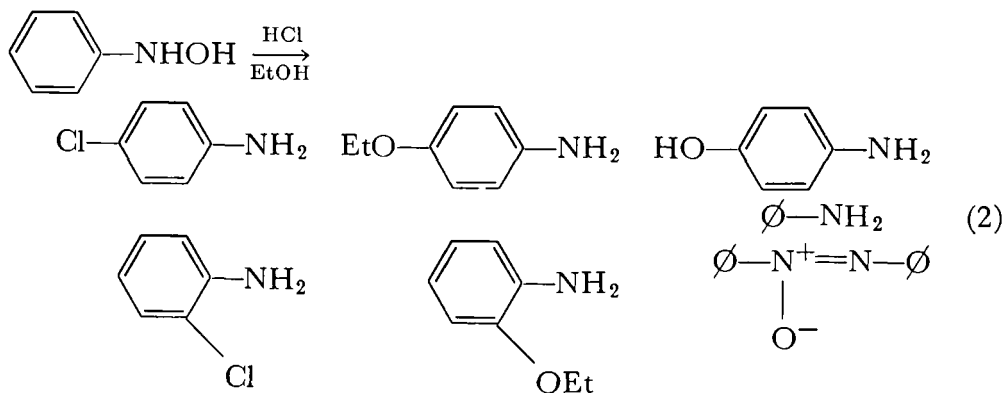
REACTIONS

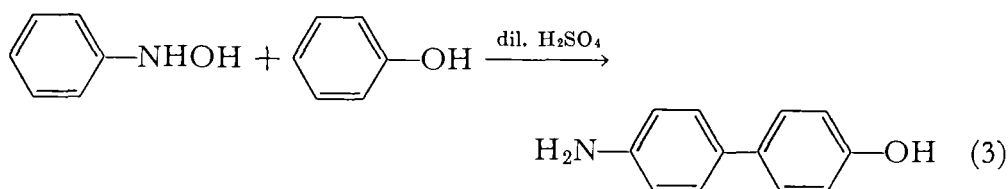
HEAT AND STORAGE The stability of hydroxylamines to heat or storage depends considerably on the degree as well as the nature of substitution. N-substituted derivatives disproportionate more or less easily, giving the amine together with an azo or azoxy compound.⁶ The final product may actually result from a secondary reaction. Phenylhydroxylamine, for example, is slowly converted to azoxybenzene and aniline on standing, presumably through initial formation of nitrosobenzene, which condenses with unreacted phenylhydroxylamine (Eq. 1). Electron-deficient nitrogen



is apparently not involved, for *o*-hydroxylaminobiphenyl gives no carbazole, the expected product from such a path, on pyrolysis.⁷

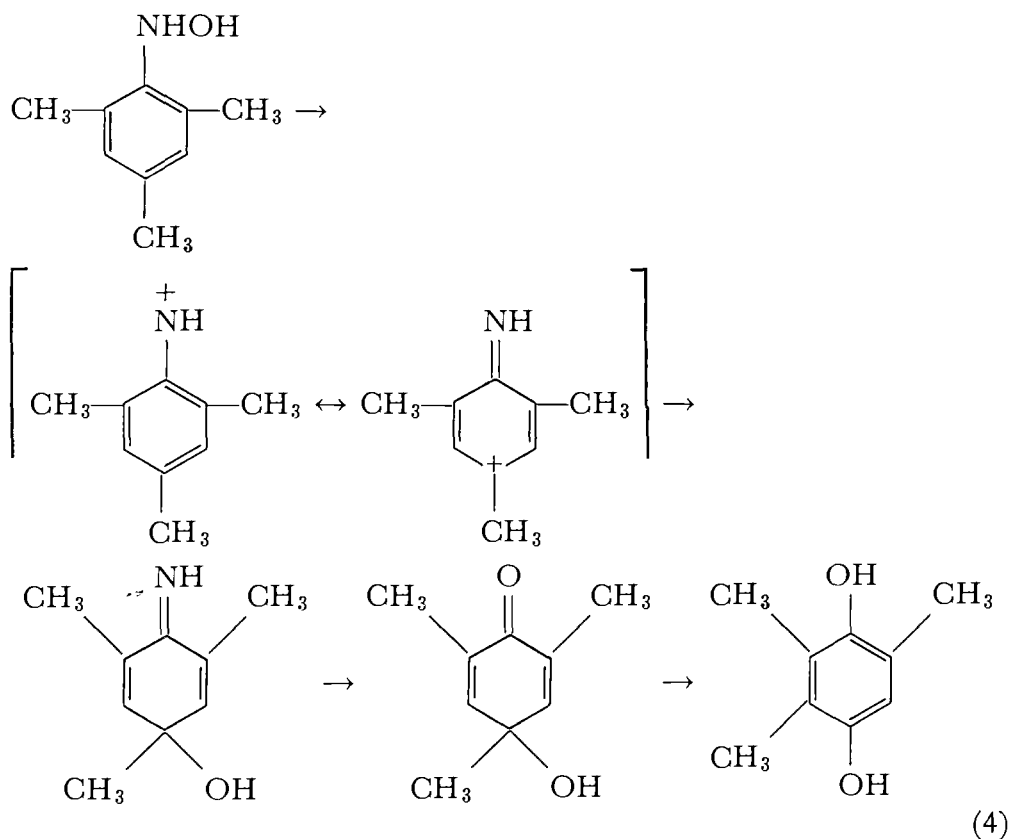
ACIDS With acids, hydroxylamines form well-defined salts, which are quite stable if there is no aryl substituent on nitrogen. Phenylhydroxylamine salts can be isolated, but they rearrange under the influence of strong acids,⁸ giving *p*-aminophenols usually accompanied by a number of related products, some of which may be colored. Since similar products are produced from aryl azides and strong acids, it was originally speculated that the azides were first hydrolyzed to hydroxylamines, but it appears more likely that an amino cation, ArNH⁺, in which the charge can be delocalized about the ring, is a common intermediate.^{8e} Rearrangement is isotopically intermolecular,^{8d} and other nucleophiles, such as halide, may be taken up to form the corresponding *o*- and *p*-substituted anilines^{8a, b, e} (Eq. 2); even phenol can serve as the nucleophile^{8c} (Eq. 3).





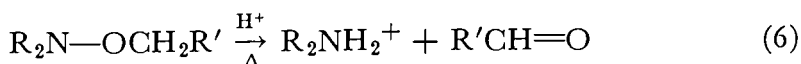
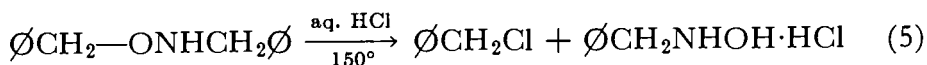
Azoxy compounds almost always accompany the rearrangement (or substitution) products and are not infrequently the principal products.⁶

Alkyl-substituted phenylhydroxylamines also form significant amounts of hydroquinones on treatment with strong acid. If the *para* position is blocked, alkyl migration takes place concomitantly. It has been shown that 4-hydroxycyclohexadienones and their imines are stages in these transformations (Eq. 4).⁸



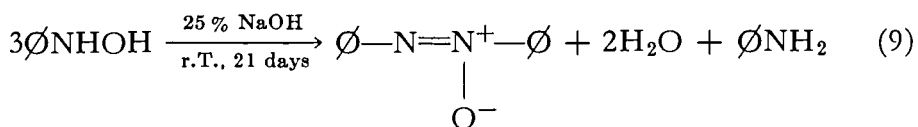
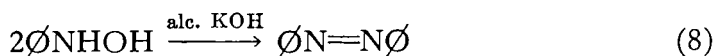
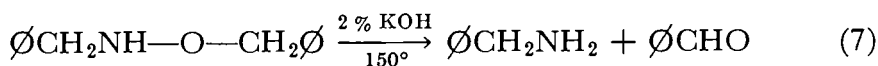
Excepting the reactions just described, hydroxylamines are nearly inert to boiling aqueous acids, and neither N- nor O-substituents are easily removed by hydrolysis. Under more drastic conditions, however, O-alkyl groups are removed through two competing processes: C—O cleavage to give a hydroxylamine (Eq. 5), and N—O cleavage to give an amine and carbonyl compound⁹ (Eq. 6). N,N-Diphenyl-O-tritylhy-

droxylamine is probably a special case; ethereal HCl cleaves it, producing

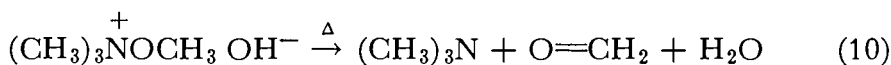


diphenylamine, *p*-trityltriphenylmethyl chloride (presumably derived from $\text{Ø}_3\text{C}^+$), and other products.¹⁰

BASES Less is known about the susceptibility of hydroxylamines to base-catalyzed cleavage.¹¹ They are generally inert under ordinary treatment, but under more vigorous conditions, O-substituents are in some cases cleaved off as aldehydes,^{11a} analogous to the result of drastic acid-catalyzed hydrolysis (Eq. 7). When there is no O-substituent, dehydration may be brought about, as in the case of N-phenylhydroxyl-

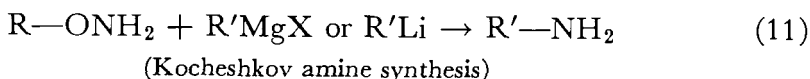


amine ^{11b} with alcoholic alkali (Eqs. 8, 9), or disproportionation to equimolar amounts of azoxy compound and amine may occur with strong aqueous base. Quaternary hydroxylammonium salts are decomposed by heating with strong base in a manner closely analogous to the Hofmann elimination of quaternary ammonium hydroxides. Elimination occurs between the oxygen and the α -carbon of the O-substituent, forming a tertiary amine and an aldehyde ^{11c} (Eq. 10).

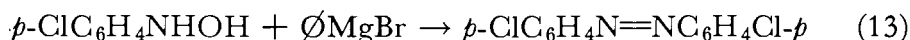
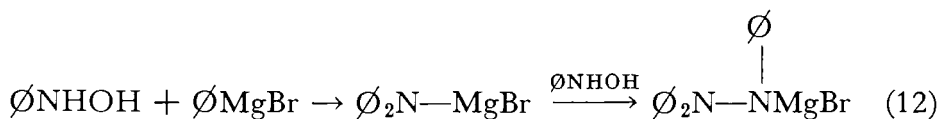


ORGANOMETALLIC REAGENTS Although hydroxylamines are unaffected by ordinary nucleophiles, they are susceptible to attack by Grignard reagents and organolithium compounds. The reactions result in cleavage of the N—O bond, and may be at least formally considered as nucleophilic displacements on nitrogen. At the same time, there is, of course, much destruction of Grignard reagent by acidic hydrogens present, and for this reason, O-alkyl derivatives are preferred when a preparative purpose is in view. Methoxyamine and the more conveniently handled benzyl-oxyamine have been recommended for the preparation of primary amines

from organometallic reagents¹² (Eq. 11). Although it is unlikely that

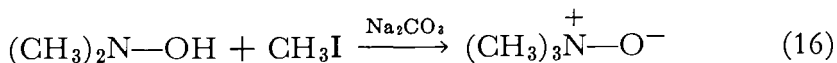
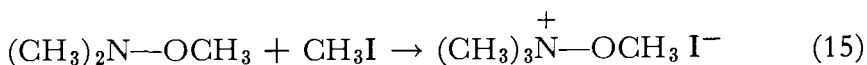
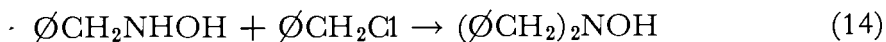


such a poor leaving group as RO^- is displaced as such in these reactions, prior coordination of the metal atom with the oxygen would allow the same overall effect to be achieved, and it seems not unlikely that the process involves a four-center transition state involving O, N, Mg, and R'. N-Phenylhydroxylamine apparently undergoes a similar but more complex reaction. The product from reaction with phenylmagnesium bromide is triphenylhydrazine,¹³ presumed to arise as a result of a second displacement involving the product of the first (Eq. 12). On the other hand, *p*-chlorophenylhydroxylamine undergoes simple dehydration,^{13c} the



Grignard reagent apparently acting only as a strong base (Eq. 13).

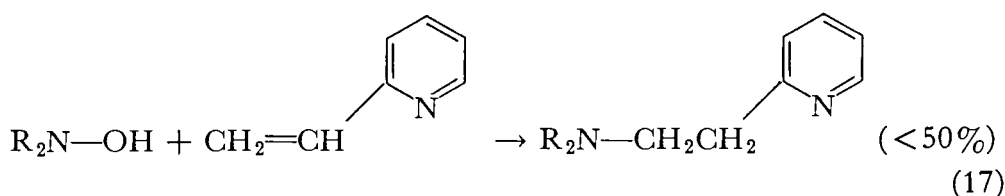
ALKYLATION Alkylating agents attack hydroxylamine and its alkyl derivatives exclusively at the nitrogen atom, as long as excessive steric interference is absent (Eq. 14). Such substitution can be continued until quaternary hydroxylammonium salts or amine oxides are produced¹⁴ (Eqs. 15, 16). Such behavior is, of course, a normal result of the relative nucleophilicity of N and O. O-Alkylation might be anticipated as a competing reaction under strongly alkaline conditions, where the oxyanion, $\text{R}_2\text{N—O}^-$, could be involved, or when alkylation is brought



about by other than a displacement reaction. Alkylation with activated olefins, such as acrylic acid derivatives, has been reported variously to give only O-substitution,^{15a,b} or only N-substitution.^{15c}

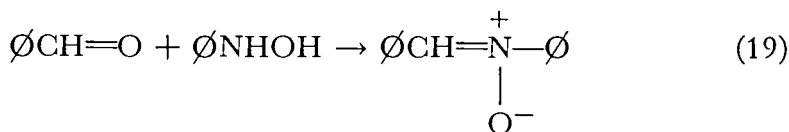
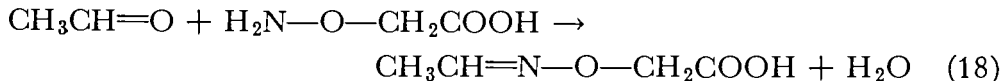
Alkylation with 2- or 4-vinylpyridine results in an unexpected reaction, producing an amine instead of a hydroxylamine; the fate of the lost oxygen has not been determined^{15a} (Eq. 17). Formation of amines has

been observed in some instances from alkylation with alkyl halides also.

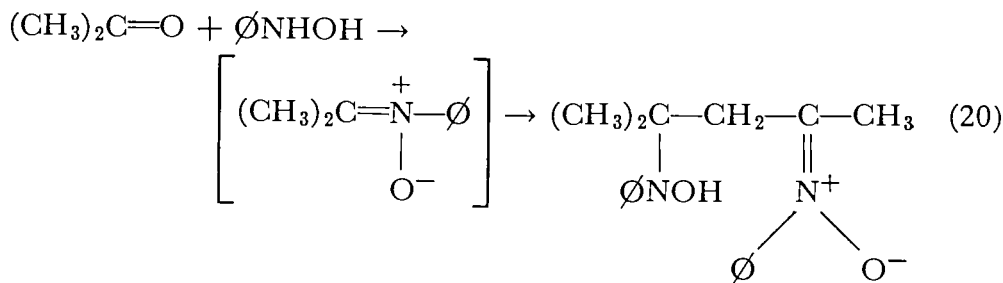


N,N-Dibenzylhydroxylamine, for example, has been reported to give only tribenzylhydroxylamine by reaction with benzyl chloride in warm ethanol,^{15b} but when heated with neat benzyl chloride, it is reported to form mono-, di-, and tribenzylamine, in addition to mono- and tribenzylhydroxylamine and benzaldehyde.⁹ The formation of the last compound presumably accounts for the "lost" oxygen.

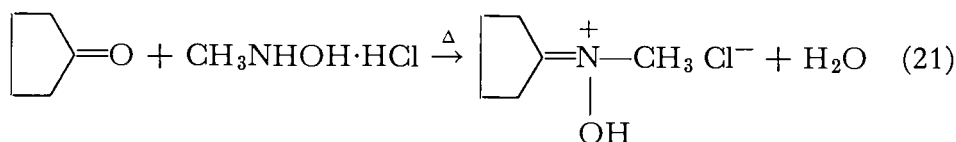
ALDEHYDES AND KETONES Hydroxylamines with at least one hydrogen left on nitrogen react with aldehydes, and in some cases with ketones; N,N-disubstituted hydroxylamines are inert. O-Monosubstituted hydroxylamines give O-substituted oximes, as illustrated by the reaction of aminoöxyacetic acid with acetaldehyde¹⁶ (Eq. 18). N-Monosubstituted hydroxylamines react readily with aldehydes to give nitrones¹⁷ (Eq. 19)



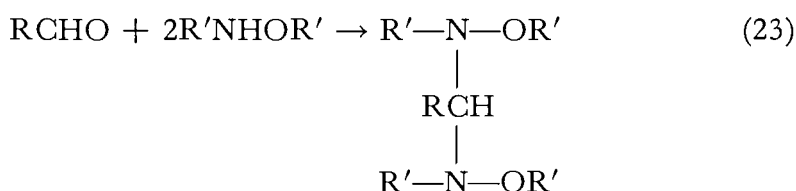
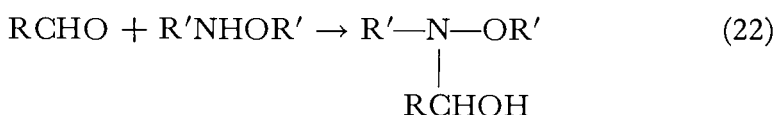
or methylene-*bis*-hydroxylamines,^{17c} but less readily with ketones. Phenylhydroxylamine and acetone form a dimeric product, which results from an aldol-like condensation of the nitrone presumed to be formed initially^{17b} (Eq. 20). It was thought for a long time that such condensation was unavoidable, ketones with no α -hydrogens being too hindered to react at all. It was later found,^{17d} however, that nitrone formation occurred



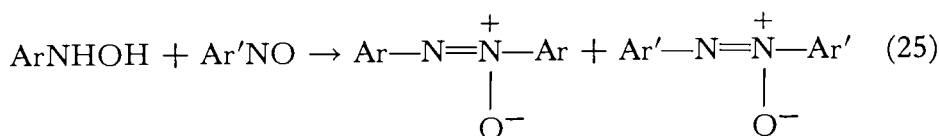
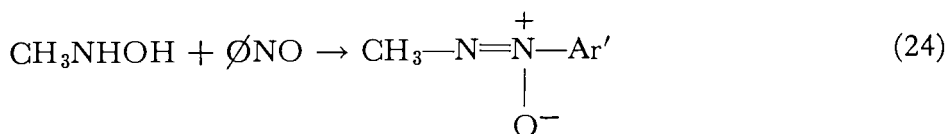
normally, without subsequent dimerization, if the environment was acidic. Heating N-methylhydroxylamine hydrochloride with dry aliphatic ketones, or the acetals of the less reactive aryl ketones, produces nitron hydrochlorides smoothly (Eq. 21). O,N-Disubstituted hydroxylamines react with aldehydes to form carbinolamine derivatives, which are unusual



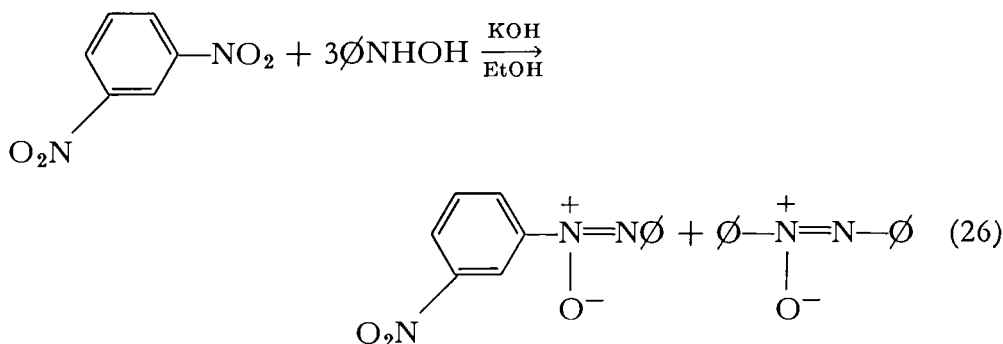
in that they are distillable, or *gem-bis*-(hydroxylamines), depending on the ratio of the reactants¹⁸ (Eqs. 22, 23).



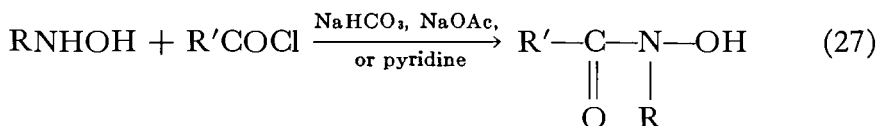
NITROSO COMPOUNDS The reactions of nitroso compounds with N-monosubstituted compounds are analogous to the reactions of aldehydes; instead of nitrones, the isosteric azoxy compounds are produced^{19a} (Eq. 24). The reactions are spontaneous and may be exothermic. When aryl hydroxylamines and nitrosobenzenes are used, disproportionation occurs, resulting in pairs of symmetrical azoxy compounds (Eq. 25). Since the unsymmetrical azoxy compounds, once produced, do not so readily disproportionate, the cause is probably to be sought in rapid interconversion between $\text{Ar}-\text{NO}$ and $\text{Ar}'-\text{NHOH}$, through formation of an N,N'-dihydroxy hydrazine^{19b} or of nitroxide anion-radicals,^{19c} $\text{RNO} \cdot^-$.



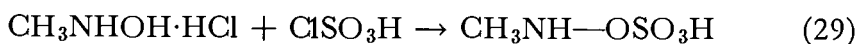
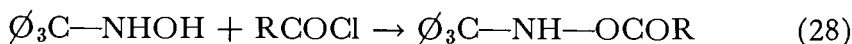
NITRO COMPOUNDS Nitro groups do not condense so readily with the —NHOH group, and indeed, many nitrosubstituted phenylhydroxylamines are known. Condensation has been observed, however, with *m*-dinitro- and 1,3,5-trinitrobenzene in basic solution^{19d}; since azoxy compounds are produced, oxidation-reduction is involved as well (Eq. 26).



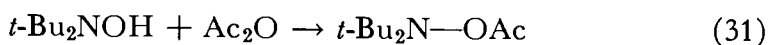
ACYLATION Acylation with anhydrides or acid chlorides ordinarily takes place on the nitrogen, if an unsubstituted position remains, giving a hydroxamic acid²⁰ (Eq. 27) or derivatives.¹⁶ With vigorous conditions, diacylation may take place (see Hydroxamic Acids, pp. 82–83). O-Acylation may occur under several circumstances; if steric hindrance or electron withdrawal deactivate the nitrogen, as in the case of *N*-trityl-



hydroxylamine²¹ (Eq. 28); if acidic conditions prevail, as in the acylation of dry hydroxylamine salts with chlorosulfonic acid²² (Eq. 29); in acylation with certain “activated esters,” such as *p*-nitrophenyl benzoate (Eq.

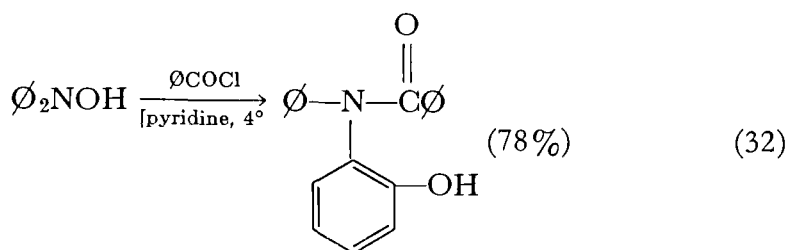


30), and with acetylimidazole,²³ and in acylation of *N,N*-disubstituted hydroxylamines^{14b} (Eq. 31).



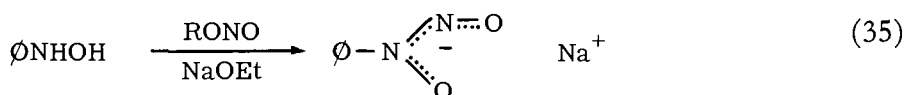
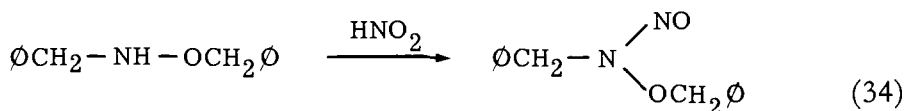
N,N-Diaryl and *N*-aryl-*N*-alkyl hydroxylamines do not react in the ordinary manner with acylating agents. *N*-Acylation takes place, and the displaced oxygen atom is either lost or is found at an *ortho* position²⁴

(Eqs. 32, 33). Since only *ortho* substitution is observed, and free radicals

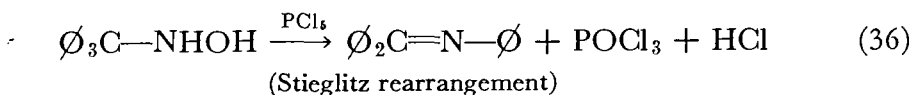


cannot be detected during the reaction, a cyclic or four-center mechanism is presumed.

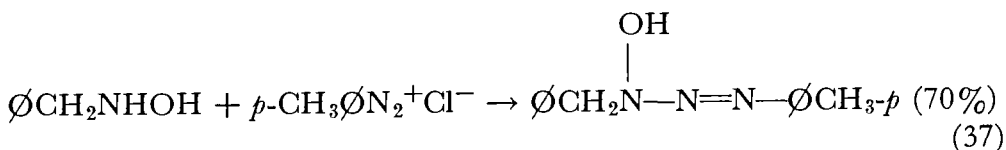
Acylation by sulfonyl halides appears to parallel that with carbonyl halides. Nitrosation also occurs readily, producing isolable N-nitroso compounds from N-monosubstituted hydroxylamines^{6b, 25}; it may be accomplished under either acidic^{6b} or basic conditions^{25a} (Eqs. 34, 35).



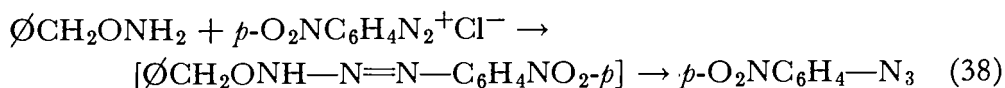
Phosphorylation is presumably effected by phosphorus pentachloride but instead of the presumed acylated derivatives, rearrangement products are formed. This is the Stieglitz rearrangement,²⁶ and has only been observed with N-triarylmethylhydroxylamines (Eq. 36) (compare the rearrangement of triphenylmethyl azide, Chapter 11).



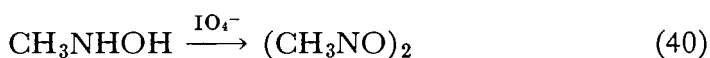
DIAZONIUM COUPLING Diazonium coupling, as is to be expected, parallels nitrosation, and occurs only at relatively strongly nucleophilic sites^{27a}; the products, 3-hydroxytriazenes, are readily isolable crystalline substances (Eq. 37). When there is no hydrogen on nitrogen, a complicated series of reactions may occur, involving free radicals and resulting in



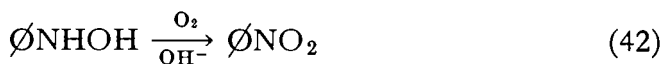
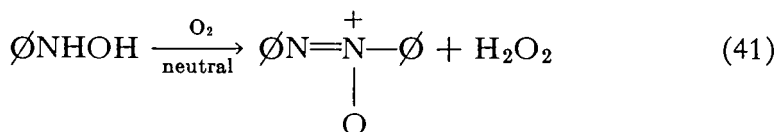
oxidative removal of an N-substituent and/or arylation.^{27b,c} Alkoxyamines, however, convert diazonium salts to azides^{27d} (Eq. 38).



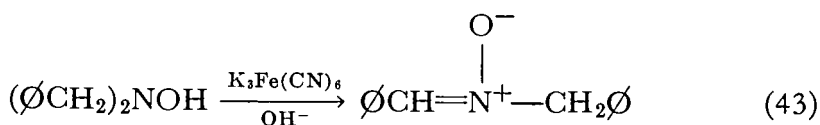
OXIDATION N-Substituted hydroxylamines are very easily oxidized, and can be expected to reduce Fehling's solution and Tollens' reagent readily, often in the cold. Monosubstituted compounds are converted to nitroso compounds (or their dimers or the isomeric oximes) by a variety of oxidizing agents,^{6b, 28} including ferric chloride, permanganate, chromic acid, periodate,²⁹ bromine,³⁰ air, etc. (Eqs. 39, 40). If the oxidation is carried out slowly, however, the nitroso compound may condense



with hydroxylamine not yet oxidized, forming azoxy compounds, which resist further oxidation (Eq. 41). On the other hand, oxidation may proceed all the way to nitro compound, as in the air oxidation of arylhydroxylamines in alkaline solution^{6b} (Eq. 42). Oxidation with iodine may be adapted to the quantitative determination of N-alkylhydroxylamines.²²

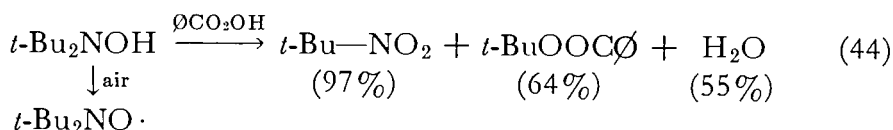


N,N-Disubstituted hydroxylamines are oxidized to nitroxide radicals, $\text{R}_2\text{N}-\text{O}\cdot$, in the first stage of oxidation (see pp. 104–107); when neither substituent has an α -hydrogen, these substances can often be isolated.^{17b, 31} Alkyl derivatives, however, are usually oxidized further, with loss of an α -hydrogen and the formation of nitrones³² (Eq. 43); the intermediate radicals appear to be of more than fleeting stability, but for the most part have been detected only by interception^{27b,c} or by electron-spin



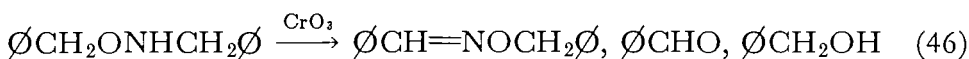
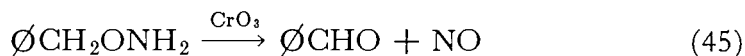
resonance.³³ Several disubstituted hydroxylamines having no α -hydrogens, such as *t*-Bu₂NOH, have been investigated^{14b, 31b}; with air or silver oxide, isolable nitroxides are formed, but with peroxybenzoic acid, a

tertiary butyl group is eliminated, and *tert*-nitrobutane is formed in high yield (Eq. 44). The latter process has been suggested to involve initial

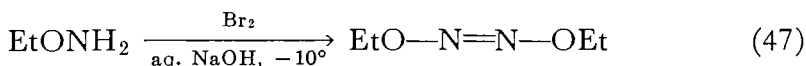


addition of an oxygen to the nitrogen, followed by rearrangement and solvolysis of the species $\text{R}_2\text{N}(\text{OH})\text{O}^-$ so produced.

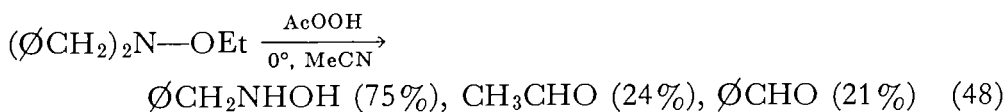
O-Substitution significantly depresses the susceptibility of hydroxylamines to oxidation, and alkoxyamines will not usually react with Fehling's solution or Tollens' reagent. O,N-Dimethyl- and O,N-diethylhydroxylamine have been reported ³⁴ to be inert to oxidizing agents, and tribenzylhydroxylamine is even inert to chromic anhydride. O-Benzyl- and O,N-dibenzylhydroxylamine, although also inert to Fehling's solution, are reactive enough to be attacked by CrO_3 (Eqs. 45, 46),^{35a} and O-alkyl hydroxylamines have been reported to be generally susceptible



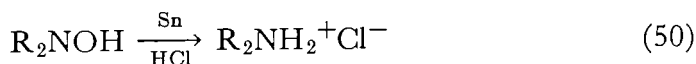
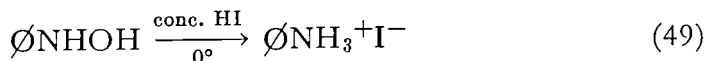
to oxidation to alkyl hyponitrites by a variety of oxidizing agents ^{35b} (Eq. 47). N,N-Dibenzyl-O-ethylhydroxylamine, on the other hand,



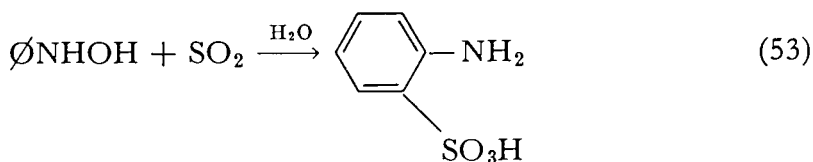
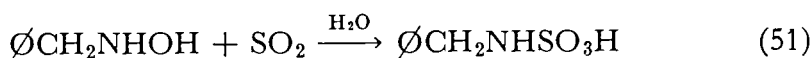
is dealkylated by peroxyacetic acid, presumably by initial attachment of an oxygen to nitrogen to form a hydroxylamine-N-oxide ^{14b} (Eq. 48).



Hydroxylamines are not nearly so readily reduced as they are oxidized. They are sometimes reduced by lithium aluminum hydride, often with migration of a group from an α -carbon to the nitrogen.³⁶ Concentrated hydriodic acid ³⁷ converts hydroxylamines to amines, in some cases even at 0° , however (Eq. 49). Tin and hydrochloric acid accomplish the same result ³⁸ (Eq. 50). Sulfur dioxide also reduces hydroxylamines, but in a different way; with N-alkylhydroxylamines as with hydroxylamine itself, sulfamic acids are produced ³⁹ (Eq. 51). Phenylhydroxyl-



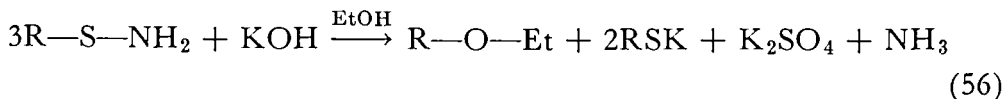
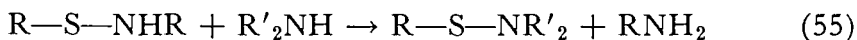
amine behaves similarly with ethereal sulfur dioxide, but in aqueous medium, orthanilic acid is formed (Eqs. 52, 53), perhaps as a result of acid-catalyzed conversion initially to O^+NH , which could combine with bisulfite ion at an *ortho* position to yield the product (cf. the Piria reaction, Chapter 13). Reduction by the Grignard reagent has been reported in



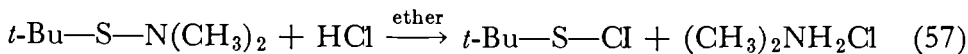
one case ⁴⁰ (Eq. 54).



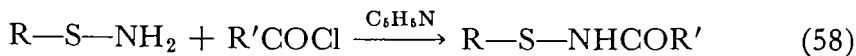
HYDROSULFAMINES It is convenient to consider the reactions of hydrosulfamines separately, since they are in several ways different from those of their oxygen analogs. Nearly all of the known examples bear a substituent on the sulfur, and thus are sulfenamides.⁴¹ The literature is sparse, and much of it is in the form of patents, owing to the use of sulfenamides as vulcanization accelerators and fungicides. The sulfur is evidently an electrophilic center. The amino group exchanges with other amines fairly readily ⁴² (Eq. 55), and alkali releases ammonia with the ultimate formation of secondary products derivable in a logical manner from the sulfenate ion presumably first formed ⁴³ (Eq. 56). Sulfenamides do not appear to react with dilute aqueous acids, but dry hydrogen bromide or chloride cleaves them exothermically to sulfenyl



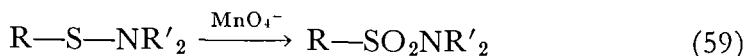
halides and amine salts ⁴⁴ (Eq. 57).



Aldehydes react with unsubstituted sulfenamides analogously to alkoxyamines and produce S-substituted thiooximes.⁴⁵ Acid chlorides also react normally,⁴⁶ in spite of the weak basicity of the sulfenamides (Eq. 58).



Oxidizing agents attack the sulfur atom of sulfenamides, converting them smoothly to sulfonamides⁴⁷ (Eq. 59). Because of the availability of many sulfenamides from mercaptans (see "Preparation"), this can be a useful synthetic route to sulfonamides.



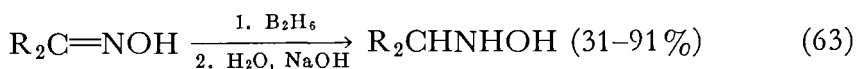
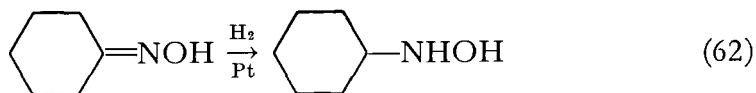
PREPARATIVE METHODS

RNHOH Monosubstituted hydroxylamines are most generally prepared by the reduction of nitro compounds (aromatic or aliphatic); zinc is the common reducing agent, and must be used in solutions kept near neutral (aq. ammonium chloride)^{6b, 48} (Eq. 60). Although this method is quite general, it is frustratingly erratic, and may be entirely unsatisfactory in some cases owing to the trouble in separating the hydroxylamine from other reduction products. Alternatively, electrolytic reduction,^{49a}



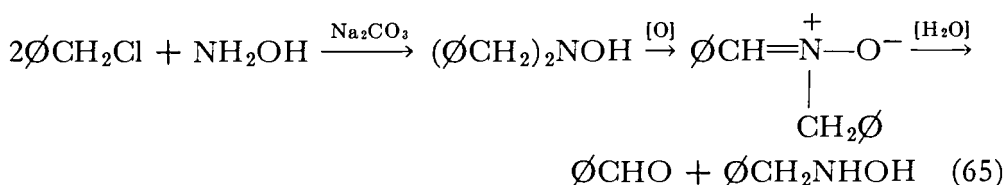
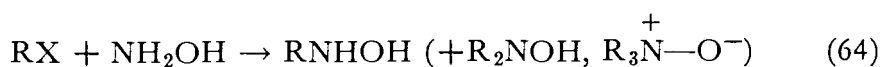
catalytic hydrogenation (Pt/C, Pd/BaSO₄),^{20, 49b} and reduction with aluminum amalgam²² (Eq. 61) or sodium sulfide^{49c} are frequently of value (see Chapter 14 for further information).

Reduction of oximes can be a useful preparative method for hydroxylamines, although it was only comparatively late that it was learned how to avoid the ordinarily overwhelming reduction to amines. Catalytic hydrogenation over a platinum catalyst in the presence of acid is successful in a few instances, notably cyclohexanone oxime (Eq. 62), but is not general.⁵⁰ Diborane, however, appears to be a generally successful reducing agent for this purpose and gives good yields⁵¹ (Eq. 63).

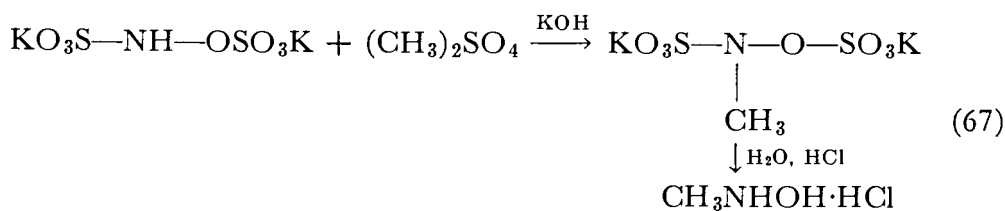
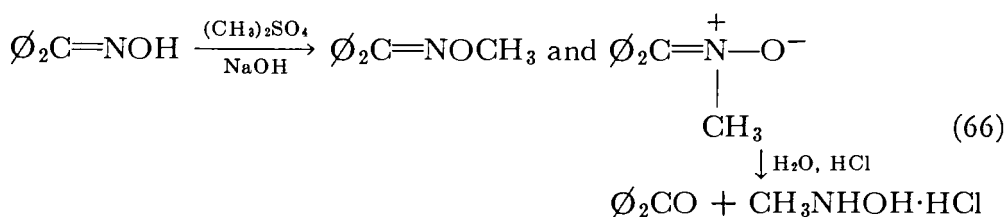


Alkylation of hydroxylamine, in aqueous or aqueous-alcoholic solution, has occasionally been used to prepare monosubstituted hydroxylamines,^{26a} but suffers from the difficulty of avoiding further alkylation (Eq. 64). It has sometimes been found more satisfactory to deliberately promote dialkylation, and then to remove one alkyl group by oxidation

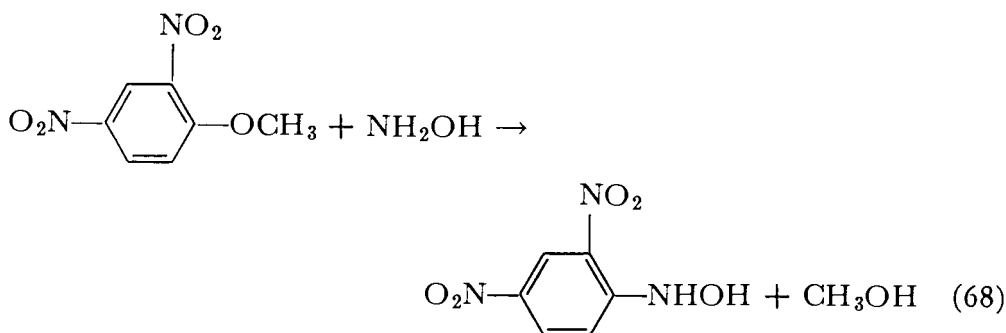
to a nitron and hydrolysis ³² (Eq. 65). Nitrones for this purpose can also be obtained by direct alkylation of oximes; although the nitron is



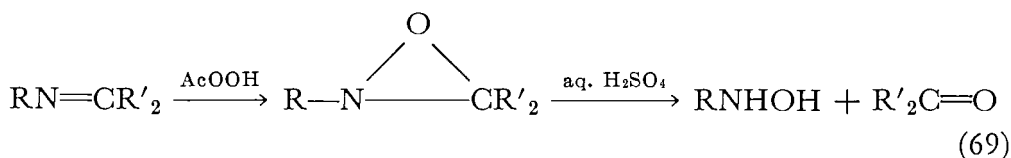
frequently the lesser product of alkylation (see pp. 44–45), separation from the isomeric O-alkyl oxime is often easy, and the overall process has much preparative value, especially when the alkylating agent is abundant ^{52a} (Eq. 66). Alkylation beyond the first stage can also be prevented by the use of acyl groups as blocking agents; hydroxylamine-O,N-disulfonic acid has been used for the purpose ^{52b} (Eq. 67). Arylation



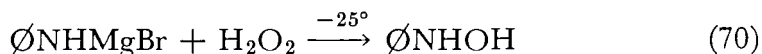
of hydroxylamine by suitably activated benzene derivatives gives mono-aryl hydroxylamines directly ⁵³ (Eq. 68).



Although oxidation in principle leads from primary amines to mono-substituted hydroxylamines, it is not a useful preparative method because of the difficulty of stopping the process, arising from the fact that the hydroxylamines are more active reducing agents than the amines. This difficulty can be circumvented in some cases by first converting the amine to an alkylidene derivative, which can then be oxidized to an oxaziridine by peroxy acids; oxaziridines are readily hydrolyzed to hydroxylamines⁵³ (Eq. 69). Direct oxidation has been accomplished successfully in a few

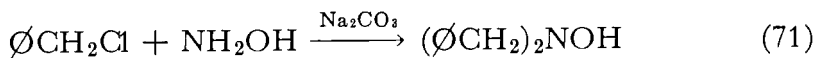


cases by treatment of the magnesium salts of anilines with anhydrous hydrogen peroxide, but it does not appear to be a generally useful method⁵⁴ (Eq. 70).

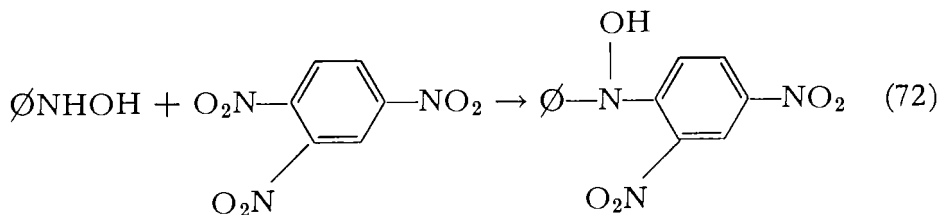


Grignard reagents can be used in special cases to prepare monosubstituted hydroxylamines by reaction with nitrosyl chloride. Yields are low, however, and the predominating products are nitroso compounds or N,N-disubstituted hydroxylamines derived from them by further addition of Grignard reagent.^{14b}

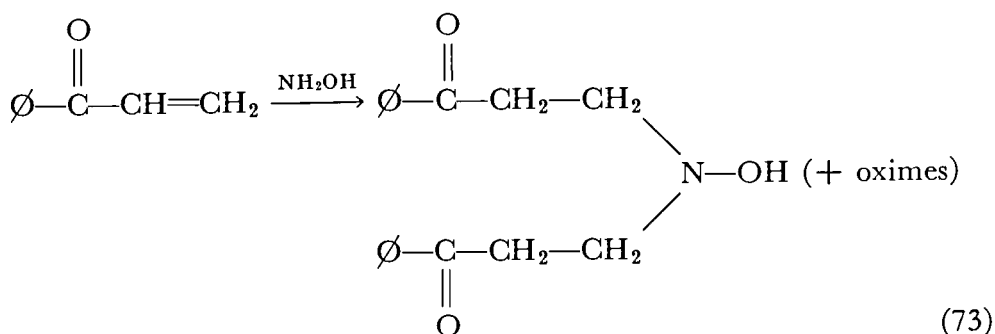
R_2NOH N,N-Disubstituted hydroxylamines can be prepared by controlled alkylation of hydroxylamine or N-monosubstituted hydroxylamines^{32, 55}; the incursion of further alkylation to form amine oxides becomes less important as the alkylating agent becomes larger (Eq. 71). Even N,N-diaryl hydroxylamines can be prepared in such a manner if



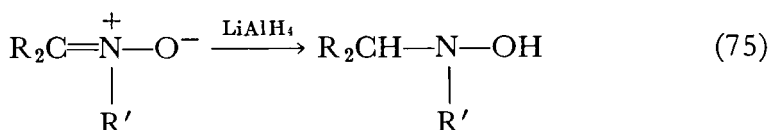
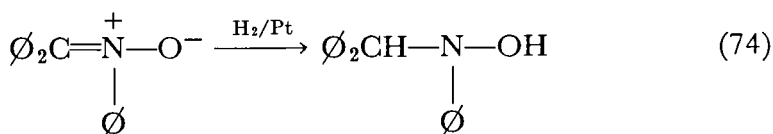
benzene derivatives activated toward nucleophilic attack are used⁵⁶ (Eq. 72). Substitution can also be brought about by suitably activated



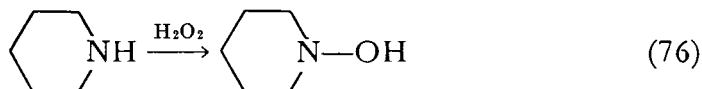
olefins, such as α,β -unsaturated ketones ^{15c, 57} (Eq. 73).



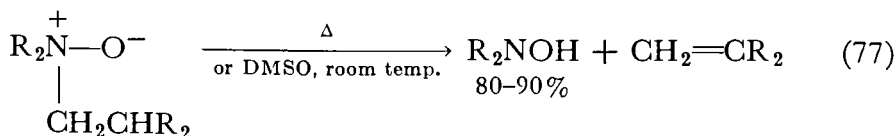
Nitrones can be reduced to hydroxylamines by either hydrogenation over platinum,⁵⁸ or by lithium aluminum hydride⁵⁹ (Eqs. 74, 75). The value of such reactions for synthesis is, of course, limited by the availability of nitrones (see section on Oximes and Derivatives).



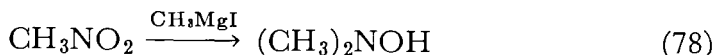
Oxidation of secondary amines with peroxides is a quite general preparative method for N,N-disubstituted hydroxylamines⁶⁰ (Eq. 76) and is particularly useful because of its simplicity. Although it is successful with a wide variety of aliphatic amines, it fails, strangely enough, with the simplest member, dimethylamine.



Another general method is the Cope elimination reaction of amine oxides; an olefin is ejected by heat⁶¹ or at room temperature in dimethyl sulfoxide,⁶² leaving an N,N-disubstituted hydroxylamine (Eq. 77). When the amine oxide contains more than one kind of substituent, the choice of which is to become eliminated as olefin parallels the Hofmann rule for eliminations in quaternary ammonium hydroxides. This reaction provides the best preparation of N,N-dimethylhydroxylamine.



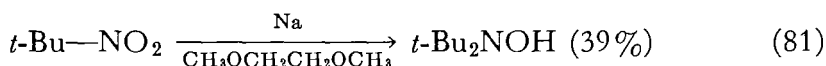
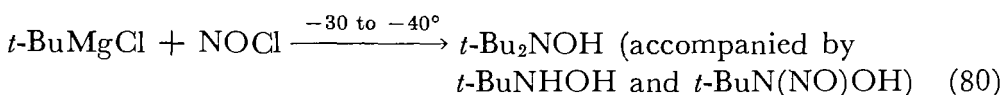
Grignard reagents can be used to prepare N,N-disubstituted hydroxylamines in several ways. Aliphatic nitro compounds form an adduct, which is reduced by excess Grignard reagent to form a dialkylhydroxylamine^{14b, 63} (Eq. 78). Nitroso compounds give disubstituted hydroxyl-



amines with only one mole of Grignard reagent^{40, 63}; this method is particularly useful for N,N-diaryl hydroxylamines (Eq. 79). A similar

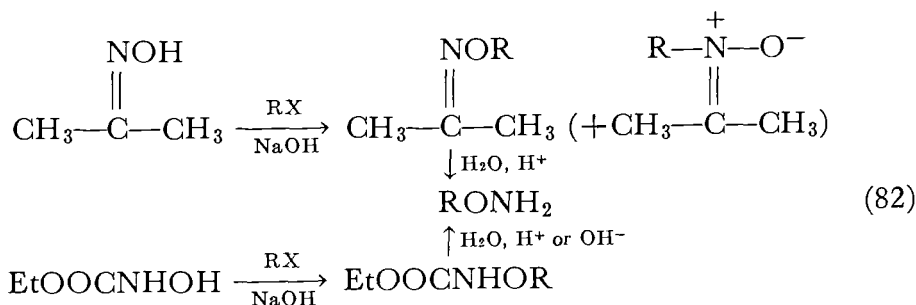


result can be obtained by preparing the nitroso compound *in situ* simultaneously, by treating a Grignard reagent with nitrosyl chloride,³⁸ or, better, by treating *tert*-nitrobutane with sodium metal in dimethoxyethane^{31b} (Eqs. 80, 81). Grignard reagents also yield dialkyl hydroxyl-



amines by reaction with nitrate esters⁶⁴ (cf. Chapter 15).

RONH_2 O-Substituted hydroxylamines, alkoxyamines, are usually prepared by alkylation and hydrolysis of salts of oximes⁶⁵ or hydroxamic acids^{16, 65}; acetoxime and N-hydroxyurethan⁶⁶ are the commonest substrates (Eq. 82). When oximes are used, the intermediate alkylation product must be purified to free it from minor but significant amounts of nitron. When very mild hydrolytic conditions are required, the



imido ester derivative, ethyl acethydroximate, may be used as the substrate.⁶⁷ Aryloxyamines can be made by arylation of benzhydroxamate salts with diaryliodonium salts, followed by solvolysis with alcoholic hydrogen chloride^{68a} (Eq. 83); the method fails when active aryl halides

such as 2,4-dinitrochlorobenzene are used, even when Lossen rearrangement can be avoided, owing to destruction of the O—N bond during

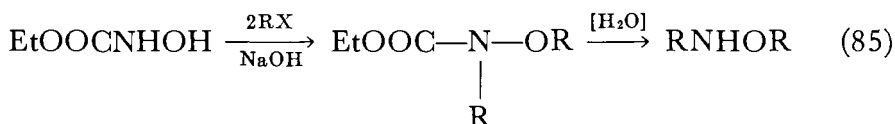


solvolysis.^{68b} Alcoholysis of chloramine^{69a} or hydroxylamine-O-sulfonic acid^{69b} (Eq. 84) provides the remaining preparative method. Sodium or potassium alkoxides or phenoxides are used. Although the yields may be very low, the reaction seems to be the most efficient route to phenoxyamines. The action of chloramine on sodium phenoxide was

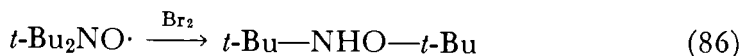


at first thought to produce phenoxyamine, but the product was later shown to be an azepinone.⁷⁰

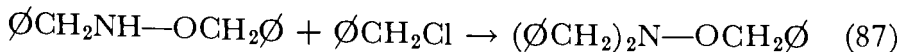
O,N-Disubstituted hydroxylamines are generally prepared⁷¹ by the hydrolysis of O,N-dialkyl hydroxamic acids, obtained by alkylation; N-hydroxyurethan is the usual substrate^{66, 72} (Eq. 85). The possibility of



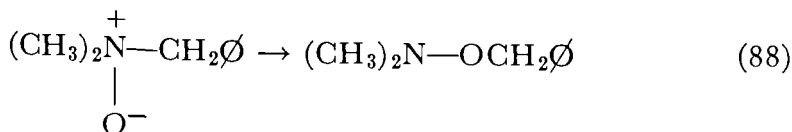
reducing O-substituted hydroxamic acids to O,N-disubstituted hydroxylamines⁷³ has not yet been exploited, nor has alkylation of alkoxyamines. The formation of O,N-di-*t*-butylhydroxylamine in small (but valuable) amounts from sodium and *tert*-nitrobutane or from di-*t*-butylnitroxide is apparently exceptional^{31b} (Eq. 86).



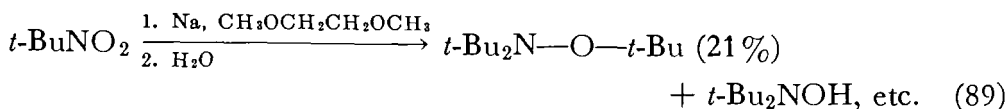
Trisubstituted hydroxylamines are usually prepared by alkylation of O- or O,N-substituted hydroxylamines, using alkyl halides^{9, 14b} or active olefins⁵⁷ (Eq. 87). In certain cases, rearrangement of amine oxides induced by heat or alkali is useful⁷⁴; the group that migrates from N to O



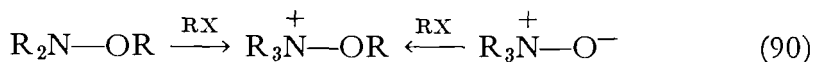
must be benzylic or allylic (Eq. 88). N,N,O-Tri-*tert*-butylhydroxylamine, which obviously could not be prepared by such reactions, has been ob-



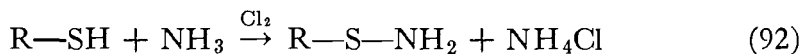
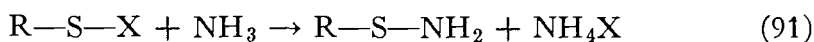
tained from the reduction products of *tert*-nitrobutane with sodium ^{31b} (Eq. 89).



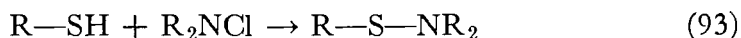
Quaternary hydroxylammonium salts can be prepared by the alkylation of either substituted hydroxylamines or amine oxides ^{11c, 75} (Eq. 90).



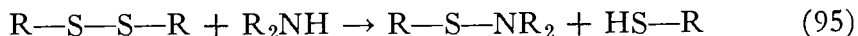
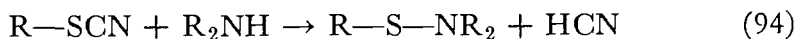
Hydrosulfamines of the sulfenamide type, $\text{R}-\text{S}-\text{NH}_2$, $\text{R}-\text{S}-\text{NHR}'$, and $\text{R}-\text{S}-\text{NR}'_2$, have most often been prepared by the aminolysis of sulfonyl halides ^{45, 46, 76} (Eq. 91). These may be prepared *in situ*, by treating a mixture of mercaptan and amine with halogen ⁷⁷ (Eq. 92).



The converse, reaction of a chloramine with a mercaptan, has also been reported ⁷⁸ (Eq. 93). Other groups than halide can be displaced from



sulfur to yield sulfenamides; examples are CN^- , in alkyl thiocyanates, ⁷⁹ and RS^- , in disulfides ⁴³ (Eqs. 94, 95). N-Substituted sulfenamides can also be obtained by aminolysis of other sulfenamides. ⁴²



AMINE OXIDES

NOMENCLATURE

Amine oxides have been named by the empirical procedure of adding the separate word "oxide" to the name of the corresponding tertiary amine, ever since the first example, trimethylamine oxide, was discovered in 1899. ^{55a, 80} The locant N- is often used for clarity, such as in "pyridine N-oxide." This crude practice has led to amine oxides being rele-

gated to an inferior status as trivial derivatives of amines by indexers, such as Beilstein and *Chemical Abstracts*, rather than being considered more properly as functional groups in their own right, or as derivatives of hydroxylamine.

PROPERTIES ⁸¹

Amine oxides are mostly solids, in some cases sirups, and are often hygroscopic and form tight hydrates. Trimethylamine oxide, mp 212°, sublimable, and triethylamine oxide, mp 96°, are extremely hygroscopic. The former forms a dihydrate, mp 96°, which requires heating in vacuum well above its melting point to drive off the water. Dimethylaniline oxide, mp 154°, does not form such a hydrate, nor do most of the larger amine oxides. The amine oxide function confers high water solubility on a molecule and strongly reduces solubility in ether and hydrocarbons; the solubility ⁸² of trimethylamine oxide in benzene at 25° is <0.03%, that of dimethylaniline oxide is 0.8%, and of pyridine oxide, >1.2%.

Amine oxides are weak bases and show the same influence of substitution on base strengths as do amines, but the range is severely compressed. The thermodynamic dissociation constants of the conjugate acids have been determined potentiometrically ⁸³: (CH₃)₃NO, pK_a 4.65; Ø(CH₃)₂NO, pK_a 4.21; Et₃NO, pK_a 5.13; ØEt₂NO, pK_a 4.53; *o*-CH₃C₆H₄(CH₃)₂NO, pK_a 4.78; *p*-CH₃C₆H₄(CH₃)₂NO, pK_a 4.32.

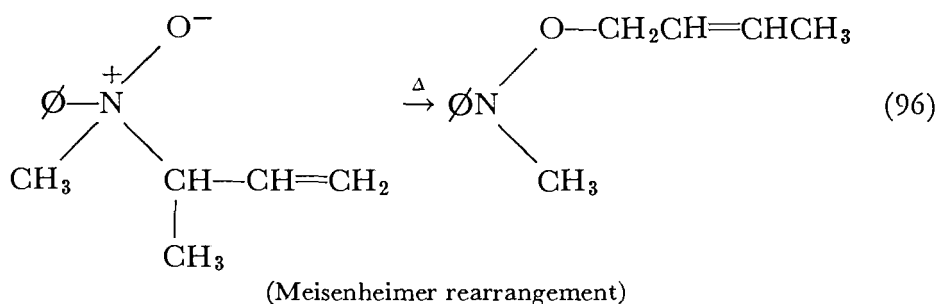
The structure of amine oxides has for a long time been accepted as that of an inner salt on the basis of their physical properties, solubility and high dipole moment.^{82, 84} Trimethylamine oxide has $\mu = 5.04$ D. in benzene solution, and dimethylaniline oxide has $\mu = 4.85$ D.; the former value is about three quarters of that calculated for a separation of charge of one full unit at the existing N—O distance. The tetrahedral arrangement of the four substituents about the nitrogen was originally deduced from the fact that suitable salts, such as methylethylaniline oxide *d*-tartrate,⁸⁵ can be resolved into optical isomers, from which optically active amine oxides can be generated. This conclusion has since been confirmed by electron-diffraction studies of trimethylamine oxide ⁸⁶ and X-ray crystallography of its hydrochloride.⁸⁷ The N—O distance in the oxide was determined to be 1.36 ± 0.03 Å, which is the sum of the single-bonded covalent radii, and that of the hydrochloride to be 1.42 Å.

The infrared spectra ^{84, 88} of several amine oxides have been observed to have a common band at 950–970 cm.⁻¹, attributed to N—O stretching.

Biochemists have been diligent in detecting the natural occurrence of trimethylamine oxide in all manner of intriguing places, such, for example, as dried squid.⁸⁹

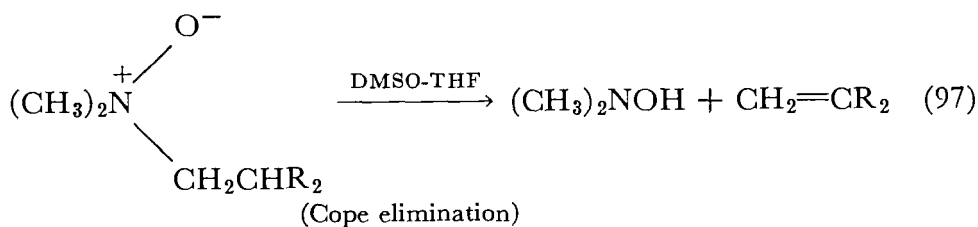
REACTIONS ^{81, 90}

THERMALLY INDUCED REACTIONS Amine oxides undergo several types of rearrangement and cleavage reactions on heating. Migration of a group from N to O takes place more or less readily if there is a benzylic or allylic group present, when the free bases are heated moderately ⁷⁴ (Eq. 96). The rate of the process is independent of added alkali and is accelerated by electron withdrawal in the migrating group. ⁹¹ By carrying



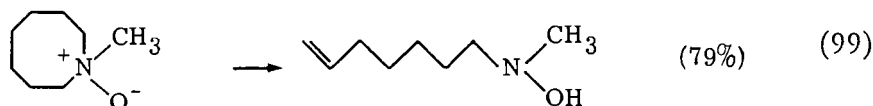
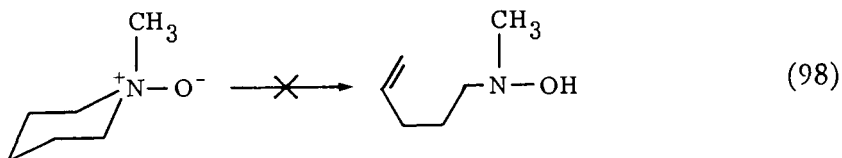
out the rearrangement of a mixture of two different amine oxides that individually have similar rates, it has been established that the rearrangement is intramolecular; no cross products, which should have resulted were the process intermolecular, could be detected. ⁹¹ When allylic groups migrate, allylic shift takes place, analogous to many other migrations of allyl groups (Eq. 96).

When there is no benzylic or allylic group on nitrogen, and there is at least one β -hydrogen, elimination of an olefin may occur. ⁶¹ Although heating is ordinarily required, the reaction may proceed even at room temperature in dimethyl sulfoxide (mixed with some water or tetrahydrofuran for solubility) ⁶² (Eq. 97); yields are high. The reaction is first order, and stereospecific in such a way as to indicate the need for a planar,

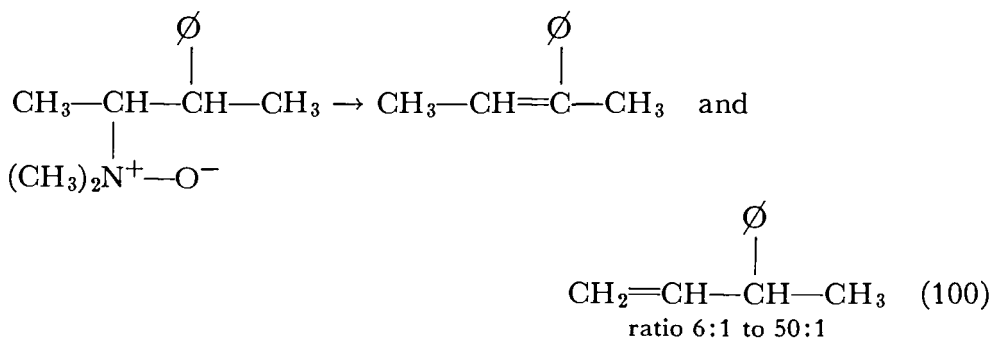


five-membered, cyclic transition state. ⁹² N-Methylpiperidine oxide, for example, does not undergo the reaction, but the corresponding compounds with seven- and eight-membered rings, where the required transition state can be reached with less strain, give 53% and 79% yields, respec-

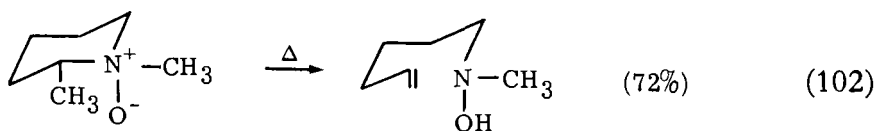
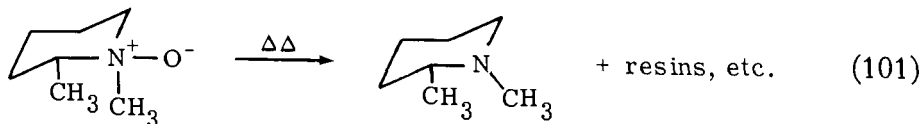
tively (Eqs. 98, 99). The process can be likened to an intramolecular Hofmann elimination, and indeed, similar factors determine the pre-



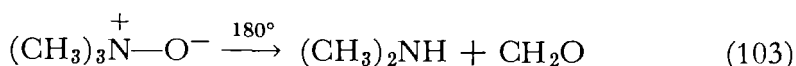
ferred site of elimination in amine oxides bearing different substituents. In the absence of strong electronic effects and the foregoing steric influences, elimination occurs most readily toward the β -position bearing the largest number of hydrogens. Activation of a β -hydrogen may be important, however, as shown by examples with a β -phenyl group, in which elimination predominantly involves the benzylic hydrogen ⁶² (Eq. 100).



When N-to-O migration and the Cope elimination are interdicted by structure, amine oxides require markedly higher temperatures for decomposition. *Cis*-N-methyl- α -pipercoline oxide, in which formation of the planar five-membered, cyclic transition states for elimination entails considerable strain, gives no hydroxylamine, but on very strong heating gives a largely intractable mixture from which some amine can be isolated; the *trans* isomer behaves normally ⁹² (Eqs. 101, 102). Trimethylamine oxide cleaves at the N—O bond, but only when heated very

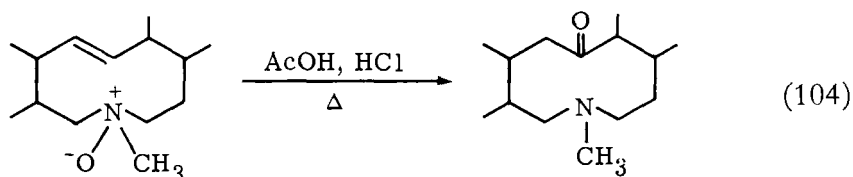


strongly ^{55a, 80} (Eq. 103). Dimethylaniline oxide behaves similarly;

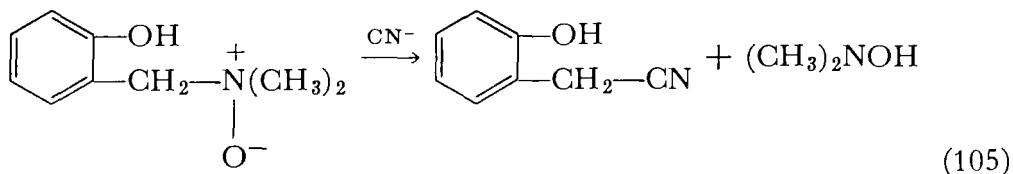


when the reaction is Bambergerized, a veritable host of minor products is found as well, including aniline, methylaniline, *bis-p*-(dimethylaminophenyl) ether, *bis*-(*p*-dimethylaminophenyl)methane, *o*- and *p*-dimethylaminophenol, *p,p'*-*bis*-(dimethylamino)biphenyl, formic acid, etc.⁹³

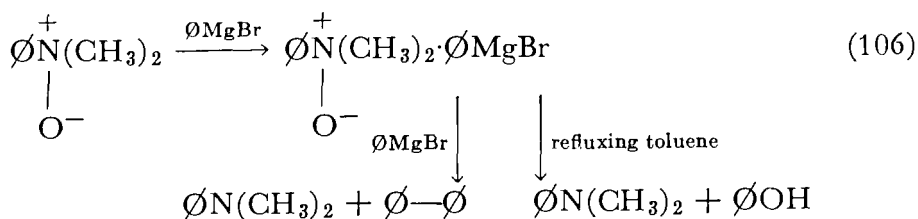
ACIDS Acids form stable, crystalline salts with amine oxides under ordinary conditions; protonation occurs on oxygen, giving an N,N,N-trisubstituted hydroxylammonium ion. When heated, such salts undergo N—O cleavage and yield products similar to those formed from the free bases. An especially interesting example involves transannular oxygen transfer to an olefinic site ⁹⁴ (Eq. 104); preparation of cyclic ketoamines in this way has played a significant role in alkaloid synthesis.



NUCLEOPHILES Amine oxides may undergo nucleophilic displacement at an α -carbon, especially if it is an activated site, as found in derivatives of Mannich bases. Cyanide, methoxide, hydride, and malonic ester carbanion have been observed to take part ⁹⁵ (Eq. 105).

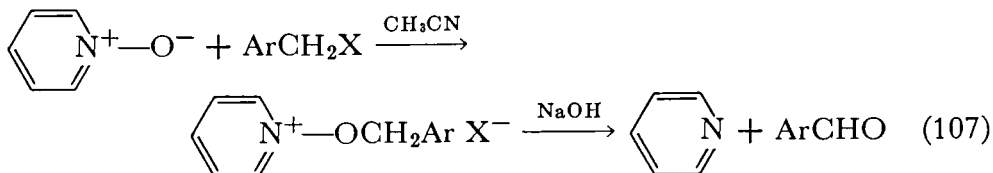


Grignard reagents form 1:1 addition complexes with amine oxides; hydrolysis regenerates the amine oxide.⁹⁵ Heating the dry complex (refluxing toluene) results in reduction to the corresponding tertiary amine and attachment of the organic part of the Grignard reagent to the oxygen; reduction is also accomplished, with a different stoichiometry, by treatment with a second mole of Grignard reagent (Eq. 106).



ALKYLATION Electrophilic reagents of various sorts not unexpectedly attack the nucleophilic oxygen site of amine oxides. Moderately active

alkylating agents, such as methyl iodide⁷⁵ and benzyl halides,⁹⁷ convert amine oxides in high yields to tetrasubstituted hydroxylammonium salts. When applied to pyridine N-oxide, this reaction makes a key part of an efficient synthesis for aromatic aldehydes, for the products can be decomposed in high yield to a tertiary amine and aldehyde by treatment with alkali (Eq. 107).

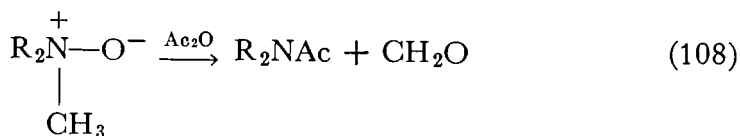


ACYLATION The initial products of the action of acylating agents on amine oxides would be expected to be O-acyl hydroxylammonium salts,

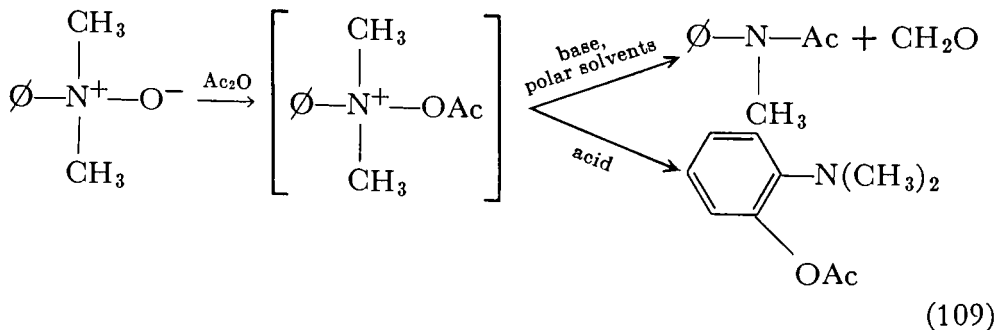
$\text{RCO}-\text{ONR}_3^+ \text{X}^-$. Although such compounds are believed to be formed generally, few are stable under the conditions customarily used. Some isolable O-acyl chlorides and chloroantimonates have been prepared from

quinuclidine N-oxide,^{98a} however, and O-sulfonates, $\text{R}_3\text{N}^+\text{OSO}_3^-$, have been isolated as extremely hygroscopic solids from the reaction of chlorosulfonic acid or oleum on amine oxides.^{22, 98b}

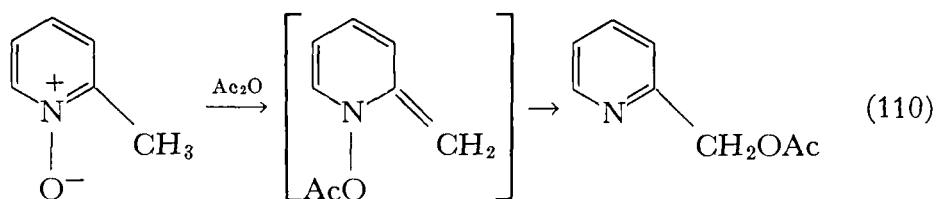
POLONOVSKI REACTION The decomposition of amine oxides on treatment with acylating agents is known as the Polonovski reaction; an alkyl group is eliminated with the oxygen as an aldehyde, and a secondary amine is formed, usually as its acyl derivative⁹⁹ (Eq. 108). When one of the substituents is aryl, as in dimethylaniline N-oxide, substitution of



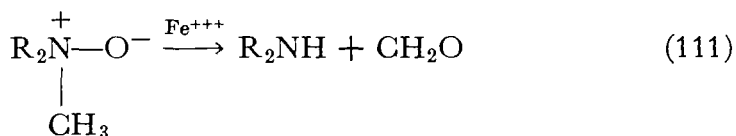
acyloxy in the *ortho* position of the ring is a competing reaction. Polar solvents and a basic environment favor the dealkylation reaction, whereas an acid environment favors the ring substitution (Eq. 109). Both reac-



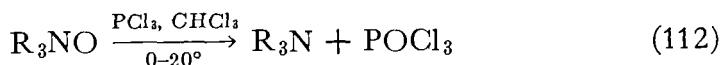
tions are believed to begin with O-acylation; base-catalyzed elimination of AcOH from the intermediate would yield an aldimmonium ion, whose acidolysis would lead to the acetamide and aldehyde.¹⁰⁰ Both homolytic cleavage of the N—O bond, and a cyclic, nonradical process have been suggested to account for the ring-substitution reaction; both paths may perhaps be significant under appropriate conditions. The related reaction with methylpyridine N-oxides,¹⁰¹ which leads to acetoxymethylpyridines (Eq. 110), has been shown to involve equilibration of the carbonyl and N-oxide oxygens in the product, which would be consistent with the intermediacy of acetoxyl radical, but the reaction is intramolecular. A radical pair intermediate has been proposed. The competing reaction, in which an acetoxy group is substituted directly on the ring,



is apparently ionic, involving nucleophilic attack by acetate ion on the O-acetyl hydroxylammonium ion. The Polonovski transformation is also brought about by treatment with ferric ion (Eq. 111). The mechanism involves a ferric ion-amine oxide complex, probably a one-electron redox step, and is believed to involve free radicals.¹⁰²



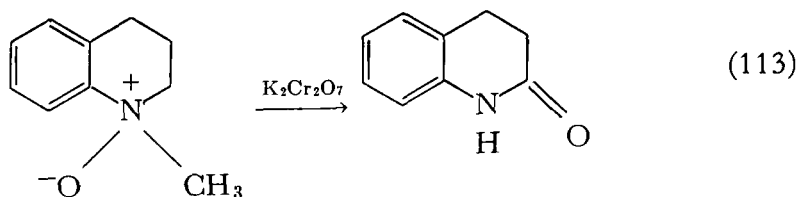
REDUCTION Deoxygenation of amine oxides to tertiary amines may be accomplished by a variety of reagents: tin and hydrochloric acid, sodium arsenite, ammonium sulfide,¹⁰³ hydrogen with a palladium catalyst,¹⁰⁴ triphenylphosphine,¹⁰⁵ various carbenes,¹⁰⁵ phosphorus trichloride,¹⁰⁷ a mixture of lead and ferrous oxalate,¹⁰⁸ etc. Phosphorus trichloride appears to be the most general (Eq. 112), and a successful reagent can nearly always be found among the collection. Hydriodic acid does not ordinarily reduce amine oxides; occasional reports to the contrary are



believed due to occluded hydrogen peroxide.¹⁰⁴

OXIDATION Amine oxides have been oxidized by chromate or dichromate to a variety of products, derived from various combinations of dealkylation and oxygenation of an α -carbon. In some cases, at least,

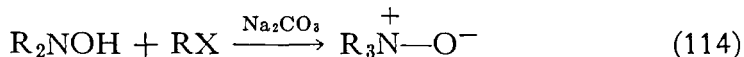
the dichromate appears to be catalytic in nature, bringing about rearrangement and disproportionation. N-Methyltetrahydroquinoline oxide, as an example, is converted to dihydrocarbostyryl ¹⁰⁹ (Eq. 113). Amine oxides are not ordinarily oxidized by Fehling's solution or Tollens'



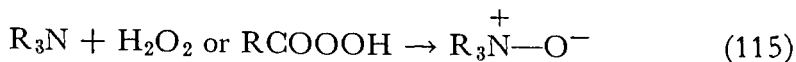
reagent, but are sometimes attacked in boiling solution.

PREPARATIVE METHODS

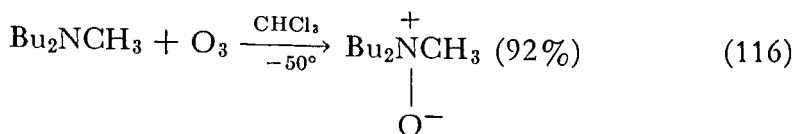
There appear to be but three reactions of significance as preparative methods for amine oxides. The oldest, exhaustive alkylation of hydroxylamine ^{55, 80} (Eq. 114), is successful with small, active alkylating agents, but is not widely used, probably because of limitations on the kind of alkylating agent that will react readily, and the fact that, for unsym-



metrical amine oxides, the mono- or disubstituted hydroxylamines then required as starting materials are somewhat troublesome to obtain. The most widely used method is the reaction of tertiary amines with hydrogen peroxide ¹¹⁰ or various peroxy acids ^{74, 91} (Eq. 115); it is usually spontaneous, and is carried out near room temperature in water, alcohol, or benzene solution. Even 3% aqueous hydrogen peroxide does quite well.



The reaction is fairly generally successful, but is markedly retarded by base-weakening effects in the amine and by any steric features that might interfere with the assumption of a tetrahedral configuration about the nitrogen atom. Finally, treatment of tertiary amines with ozone gives amine oxides, often in high yield ¹¹¹ (Eq. 116).



OXIMES AND DERIVATIVES (Including Nitrones)

NOMENCLATURE

Oximes are most generally named by adding the separate word "oxime" following the name of the parent aldehyde or ketone and are listed this way in *Chemical Abstracts*. When necessary for reasons of priority, the oxime group may be designated by the prefix "hydroxyimino," as in 2-hydroxyiminopropionic acid, $\text{CH}_3\text{C}(=\text{NOH})\text{COOH}$. It was customary in the older literature to elide the name of the ketone or aldehyde with the word oxime, to produce such names as "acetaldoxime" ($\text{CH}_3\text{CH}=\text{NOH}$) and "benzophenoxime" ($\text{C}_6\text{H}_5\text{C}_2\text{H}=\text{NOH}$); these names still find favor because of their brevity. For prefix purposes, the term "isonitroso-" was used, since oximes can often be made by isomerization of nitroso compounds; it has, unfortunately, not yet entirely faded away.

Oximes substituted on the oxygen are best named as O-alkyl (aryl, acyl) oximes, as in "acetone O-methyloxime" ($(\text{CH}_3)_2\text{C}=\text{NOCH}_3$), but a frequently encountered alternative is to name them as O-ethers, as in "acetone oxime O-methyl ether." For prefix use, the form "methoxyimino-" can be used.

N-Substituted oximes are known as a class as nitrones. *Chemical Abstracts* names them as derivatives of the hypothetical compound

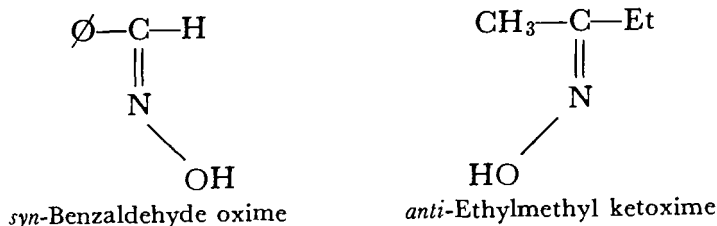
$\text{CH}_2=\overset{+}{\text{N}}\text{H}-\text{O}^-$, which is called nitrone, and lists them all under Nitrone, with inverted names. Substituents on the carbon are designated by α -, those on nitrogen by N-, as in " α,α -diphenyl-N-methylnitrone"

($\text{C}_6\text{H}_5\text{C}_2\text{H}=\overset{+}{\text{N}}(\text{CH}_3)-\text{O}^-$). The I.U.P.A.C. tentative recommendations favor the use of the word nitrone as a class name only, with names of the type "benzophenone N-methyloxime" for specific compounds. The term

"isonitrone" sometimes seen refers to oxaziridines, $\text{R}_2\text{C}-\text{O}-\text{NR}$, many of which have been isolated.

Geometrical isomers of oximes and their derivatives are usually designated by the prefixes *syn*- and *anti*-. It is, of course, necessary to make clear which group of an unsymmetrical ketone is used for reference in unsymmetrical ketones; with aldehydes, the prefix *syn*- is customarily used for those forms having the aldehydic hydrogen and the oxygen on the same side—e.g., *syn*-benzaldehyde oxime. With ketone derivatives, differentiation is conveniently made by using the ketoxime type of nomenclature, placing the substituent of reference first, as in *anti*-ethylmethyl

ketoxime. Unfortunately, most configurations were misunderstood be-



fore the 1920's, and the prefixes used in the older literature must be reversed to conform to modern conventions. The prefixes α - and β - were also often used; α - referred to those aldoximes now known as *syn*-.

PROPERTIES

Oximes are mostly colorless solids of moderate melting point, soluble in water to an extent somewhat similar to amides of the same molecular weight (formaldoxime and acetaldoxime are miscible with water). Only the smallest are appreciably volatile. Substitution of a methyl group on oxygen lowers the boiling point and the melting point, owing to the removal of the source of hydrogen bonding (see Table 8-2). Nitrones are generally less volatile, higher melting, and less soluble in nonpolar solvents than their O-substituted isomers, effects to be expected of the

high dipole moment of the N^+-O^- bond.

Table 8-2

Oxime	mp, °C	bp, °C/mm.	K_a
$\text{CH}_2=\text{NOH}$		84°	
$\text{CH}_3\text{CH}=\text{NOH}$	47° (and 13°)	115°	
$\text{CH}_3\text{CH}=\text{NOCH}_3$		47.5°	
$(\text{CH}_3)_2\text{C}=\text{NOH}$	61°	135°/728	3.8×10^{-13}
$(\text{CH}_3)_2\text{C}=\text{NOCH}_3$		74°	
$^*(\text{CH}_3)_2\text{C}=\text{N}^+(\text{CH}_3)-\text{O}^-$	oil	77°/2	
<i>syn</i> - $\text{O}-\text{CH}=\text{NOH}$	35°	118-124°/14	2.1×10^{-11}
<i>anti</i> - $\text{OCH}=\text{NOH}$	132°		0.5×10^{-11}
$\text{O}_2\text{C}=\text{NOH}$	144°		0.5×10^{-11}
$\text{O}_2\text{C}=\text{NOCH}_3$	61°		
$\text{O}_2\text{C}=\text{N}^+(\text{CH}_3)-\text{O}^-$	103°		

* Dimer or trimer?; molecular weight not determined.

Oximes are weak acids, strong enough to dissolve in aqueous sodium hydroxide, but precipitated by carbon dioxide. Simple oximes have pK_a 's in the range 10 to 12¹¹²; an α -keto group considerably increases the acid strength (pK_a 7 to 10).¹¹³ For similar reasons, α -dioximes are stronger acids than monoximes: $\text{HON}=\text{CH}-\text{CH}=\text{NOH}$, pK_a 9; dimethylglyoxime, pK_a 10.7.¹¹⁴ Aqueous solutions are just detectably acidic.¹¹⁵

Oximes also show a very weak basicity; because of the double bond, they would be expected to be several powers of 10 weaker than hydroxylamine (cf. the basicity of imines compared to amines, Chapter 7), and because of the effect of the hydroxyl group, they would be expected to be several powers of 10 weaker than imines. Most oximes are soluble in concentrated mineral acid solutions, but are in many cases largely precipitated by dilution with water; crystalline hydrochlorides can be isolated. Little quantitative information is available; the conjugate acid of acetone oxime has pK_a 1.75.¹¹⁶ Nitrones are also weak bases; they form salts that appear to be less extensively hydrolyzed than those of the corresponding oximes, from which one can conclude that the nitrones are stronger bases.^{117, 118} The O-alkyl oximes, by contrast, appear to be without basicity in water solution¹¹⁷; the effect of O-alkylation is thus parallel to that in hydroxylamines.

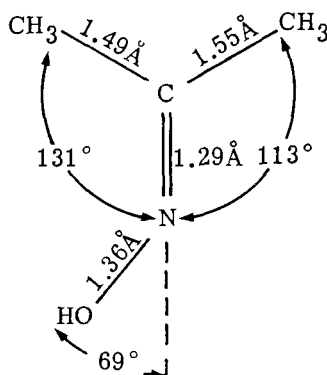
Oximes show the expected $\text{C}=\text{N}$ stretching absorption in the infrared at 1600–1665 cm^{-1} (6.0–6.25 μ)^{114, 119}; $\text{N}-\text{O}$ stretching has been located at 940–985 cm^{-1} (10.14–10.63 μ). Aldonitrones show $\text{C}=\text{N}$ stretching absorption at 1570–1590 cm^{-1} , and ketonitrones absorb at slightly higher

frequencies (1600–1620 cm^{-1})^{48b, 120, 121a}; $\text{N}-\text{O}^+$ stretching can be seen at 1170–1280 cm^{-1} , similar to amine oxides and azoxy compounds. O-Alkyl oximes show $\text{C}=\text{N}$ and $\text{N}-\text{O}$ stretching frequencies close to those of simple oximes; the $\text{C}=\text{N}$ absorption is usually at slightly higher frequency than that of the isomeric nitrone.¹²¹ Nitrones absorb moderately strongly in the ultraviolet (for nonconjugated examples,) (229–235 $m\mu$, $\epsilon \sim 9000$),^{48b} and generally at wavelengths about 50 $m\mu$ longer than do the oximes or O-substituted isomers.^{121b} The aldehydic hydrogen of aldonitrones gives a nuclear magnetic resonance signal at $\sim 4\tau$ ¹²⁰; the deshielding effect of the nitrone structure is evidently much less than that of the carbonyl groups of aldehydes.

The structure of oximes was actively debated for the first three decades of the 20th century, and it is only with the advent of physical methods that the matter has at last been resolved. The isomeric nitrone and oxaziridine structures, as well as the vinyl hydroxylamine tautomer, were for a time considered to offer explanations for the existence of the various isomeric forms encountered with some oximes and their derivatives. The

older arguments have been thoroughly reviewed by Meisenheimer and Theilacker¹²²; since then, oxaziridines have been isolated¹²³ and found to be quite distinct from nitrones, and nuclear magnetic resonance¹²⁴ has enabled most of the laboriously won conclusions of other experimental methods to be confirmed.

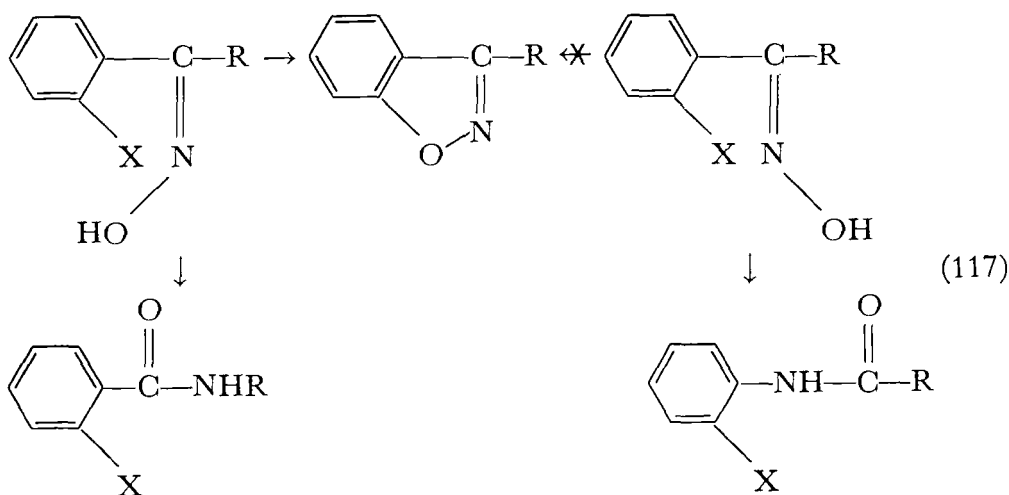
The structure of several oximes has been examined by X-ray crystallography. The following values have thus been determined for acetoxime¹²⁵: C=N, 1.29 Å; N—O, 1.36 Å; C—C(*syn*), 1.49 Å; C—C(*anti*), 1.55 Å; $\angle$ CNO, 111°; $\angle$ CCN(*syn*), 131°; $\angle$ CCN(*anti*), 113°. The profound effect of the hydroxyl group in distorting the symmetry of the rest of the molecule is noteworthy. Comparable results have been obtained with formaldoxime, *p*-chlorobenzaldoxime and dimethylglyoxime.¹²⁶



It is evident that the presence of a C=N double bond, about which rotation would be expected to be severely restricted, should lead to the possibility of geometrical isomerism in oximes in which the two groups attached to carbon are different. Unambiguous recognition of isomers arising from this was for some time obscured by uncertainties about the structure of oximes on the one hand, and by the existence of polymorphic forms of many oximes on the other.¹²² The evidence on which the correct identifications were eventually based is massive,^{122, 127} and it is not purposed to review it all here.

Geometrically isomeric oximes of a large number of aromatic aldehydes and aryl ketones have been isolated and characterized. Most of them are interconvertible; the energy differences (heats of isomerization) are naturally dependent on the structure; those for aldoximes are in the range 0.5 to 5 kcal/mole.¹²² The barrier to interconversion is also variable and for purely aliphatic, open-chain compounds is so low that only rarely can separate isomers be obtained. The O-substituted oximes and the nitrones are likewise capable of geometrical isomerism, a fact that has been confirmed by many instances of separately identified isomers.¹²²

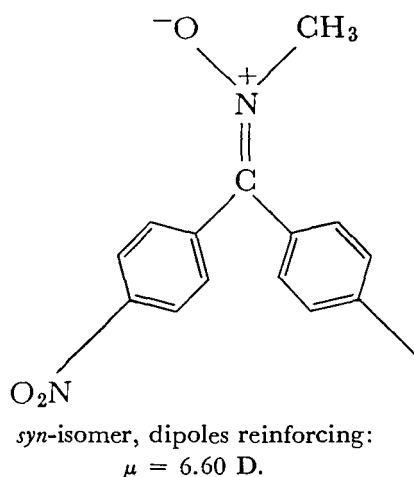
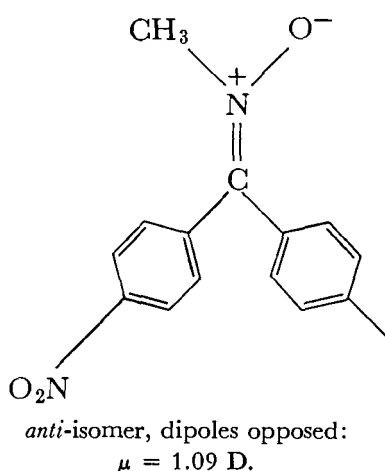
The problem of assigning configuration to geometrically isomeric oximes was for a long time a vexing one. For ketoximes, the Beckmann rearrangement^{26b, 127} was the only means available until physical methods became sufficiently developed. Its proper interpretation depended on a knowledge of the mechanism of the reaction; that knowledge was totally inadequate in the 19th and early 20th centuries, a state of affairs that led to the incorrect assumption that the *syn*-moiety of the oxime changed places with the hydroxyl and became attached to nitrogen. The result was the assignment of exactly the wrong configurations to all ketoximes. Although this situation was not unreservedly accepted, it was not upset until 1921, when Meisenheimer¹²⁸ published the first of a series of papers dealing with certain oximes whose configuration could be deduced independently, either from differences in ability to cyclize to adjacent functions (Eq. 117), or from a method of synthesis involving the opening of a ring. Although some of the experiments can now be judged to be of questionable validity, taken as a whole they presented a convincing picture that the Beckmann rearrangement proceeds by migration of the *anti*-substituent. Since about 1930, the configuration of ketoxime isomers has been interpreted on this basis and the incompletely supported assumption that all Beckmann rearrangements are alike and proceed without concurrent *syn-anti* interconversion. Most of the configurational assignments made in this way are apparently sound, for the configuration of a



considerable variety of oximes has been established less ambiguously by spectrographic methods,^{26b} and cases of interconversion of isomers under the reaction conditions have been to a considerable extent sorted out.

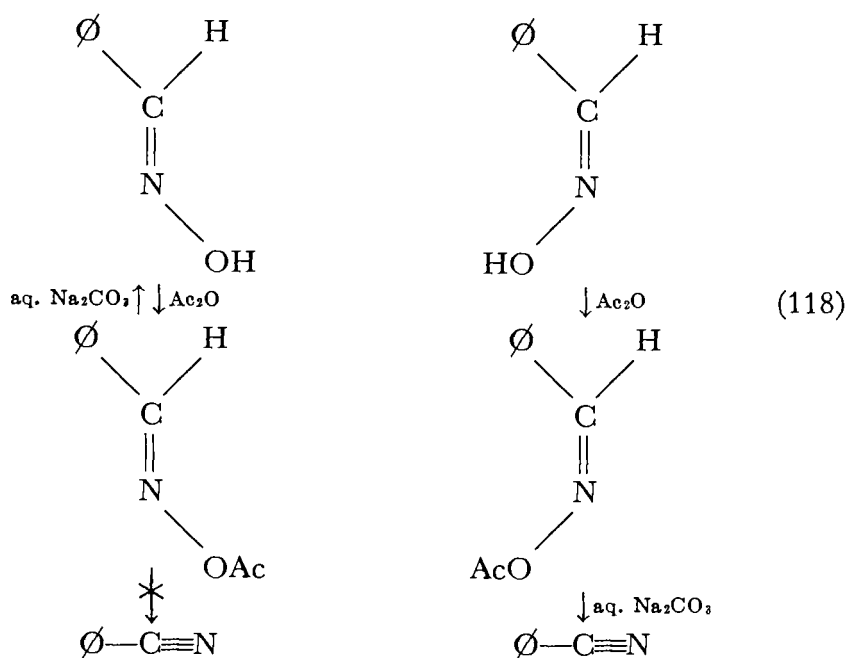
The configuration of oxime derivatives can only be investigated by the Beckmann rearrangement in the case of those bearing O-acyl groups derived from moderately strong acids. The configuration of O-alkyl

oximes has generally been assumed to be the same as that of the oxime isomer from which they have been made, on the basis of the reasonable assumption that their formation involves only a nucleophilic displacement by the oxyanion on the alkylating agent. This assumption is less convincing with nitrones, but here the high dipole of the N—O bond makes available another means of establishing configuration. Measurements of the dipole moment ^{129a} of the two isomeric N-methyloximes of *p*-nitrobenzophenone, for example, enables the configuration to be related to whether the dipole of the nitron group is roughly parallel to that of the nitro group, and thus reinforcing, or antiparallel and thus opposing. Oximes themselves have only small dipole moments.^{129b}



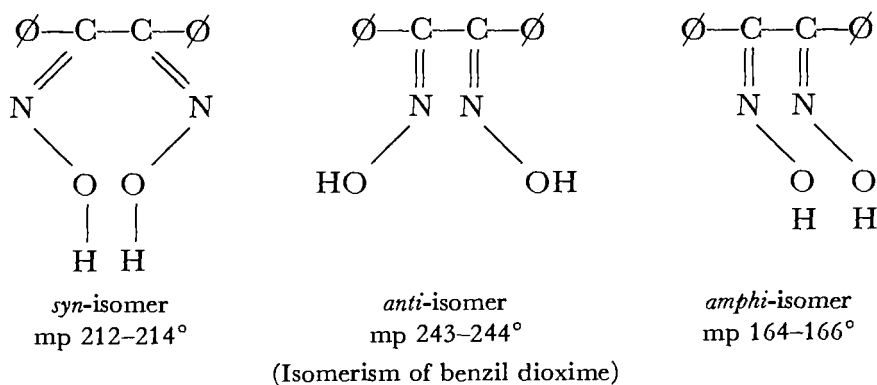
The preferred configuration (thermodynamically more stable) of ketoximes is determined by both steric and electronic factors ^{122, 130}; in saturated, aliphatic oximes, where the steric factor is the only significant one, interconversion is too rapid to permit isolation, but it is assumed that the more stable form is that with hydroxyl *syn*- to the least bulky group.

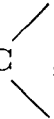
The situation with aldoximes is somewhat similar, except that it is dehydration to a nitrile rather than Beckmann rearrangement that has been used as the principal diagnostic tool. Dehydration was at first thought to involve *syn* groups (H and OH), but later shown to be a case of *trans* elimination ¹³¹ (Eq. 118). For most aldoximes, the *syn*-isomer is the more stable, presumably as a result of lower steric hindrance. The *syn*-isomers are generally stronger acids,¹¹² with the result that the heat of neutralization is greater, making the sodium salts more stable than those of the *anti*-isomers by an even greater margin. The conjugate acids, however, are often more stable in the *anti* configuration, and indeed, treatment with hydrogen chloride is the most general method for obtaining the *anti*-isomers.¹²² *syn*-Aldoximes are usually lower melting than their



anti-isomer, and do not readily form complexes with transition metal ions. The ferric chloride test, whereby some oximes give a blood-red color due to complex formation, thus often fails, although it is successful with the *anti*-isomers.

Dioximes, such as the familiar analytical reagent dimethylglyoxime, have a more ramified capability for isomerism. When the molecule is formally symmetrical, as in the example, there are three possibilities: *syn*-, *anti*-, and *amphi*-. It is the *anti*-isomer that is responsible for the formation of the brightly colored chelate derivatives with nickel and other metal ions. When the carbon skeleton is unsymmetrical, there are, of course, two different *amphi*-isomers, making a total of four, in principle possible; four have actually been isolated in several cases.¹²²

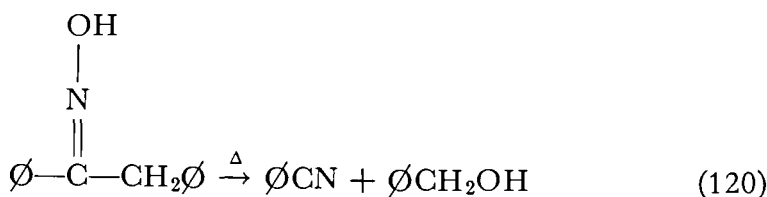
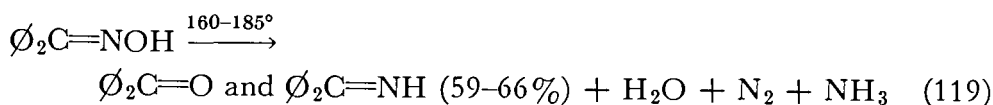


The properties of the carbohydroximido group, $\text{HON}=\text{C}$ , as an aromatic substituent are electron withdrawing and *meta* directing, at least

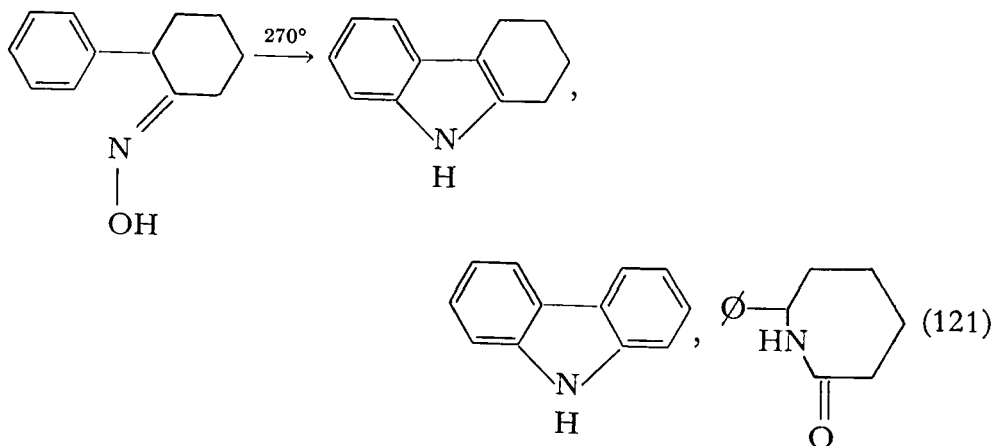
in sulfuric acid solution; O-methylbenzaldoxime is very resistant to nitration compared to its N-methyl isomer.¹³²

REACTIONS

HEAT AND STORAGE Oximes are reasonably stable substances, but their stability to storage varies considerably. Some undergo decomposition even when protected from air and light, yielding the parent carbonyl compound and mixtures of inorganic nitrogen compounds; benzophenone oxime is particularly prone to such decomposition.^{134a} Strong heating causes decomposition by several paths. Benzophenone oxime is converted into nitrogen, ammonia, benzophenone and its imine, the latter in sufficient quantities to be of preparative value ^{134a} (Eq. 119); under other conditions, little or no imine is formed.^{134b} When α -hydrogens are present, cleavage into alcohol and a nitrile may become the most important reaction (Eq. 120). 2-Phenylcyclohexanone oxime undergoes cyclization to tetrahydrocarbazole when heated; some of this product is



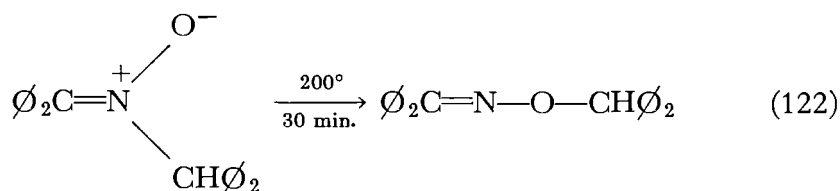
oxidized by more oxime to carbazole, and some products of Beckmann rearrangement are also formed ⁷ (Eq. 121). *anti*-Benzaldoxime gives



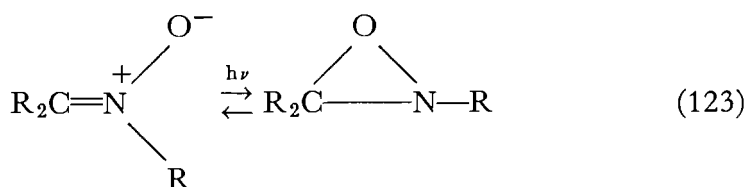
benzamide and benzoic acid on distillation.^{134c}

Nitrones are reasonably stable substances when derived from aromatic ketones or aldehydes, but aliphatic examples decompose on storage, and to a considerable extent during vacuum distillation, to form unidentified and often resinous products.^{17d} Nitrones having a benzhydryl or triphenylmethyl group on the nitrogen rearrange on heating, just as do similarly constituted amine oxides, to form the O-substituted isomers (Eq. 122).¹³⁵

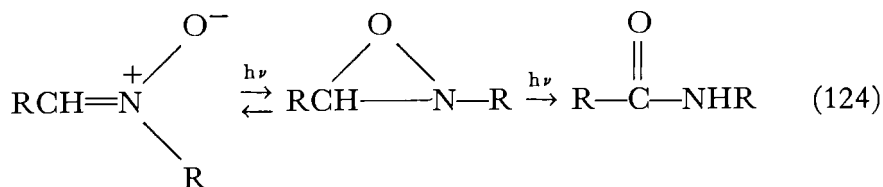
The reaction is first order kinetically and is intramolecular. Benzophenone N-benzyloxime does not undergo this rearrangement, however,



but gives products explainable by an initial cleavage into benzaldehyde and benzophenone imine.¹³⁵ A different sort of rearrangement is brought about by irradiation; the oxygen closes a ring to the carbon, forming an oxaziridine¹³⁶ (Eq. 123). The oxaziridines are of higher energy than nitrones, to which they can usually be reconverted, sometimes simply on standing in the dark.^{136a} Oxaziridines derived from aldonitrones, how-



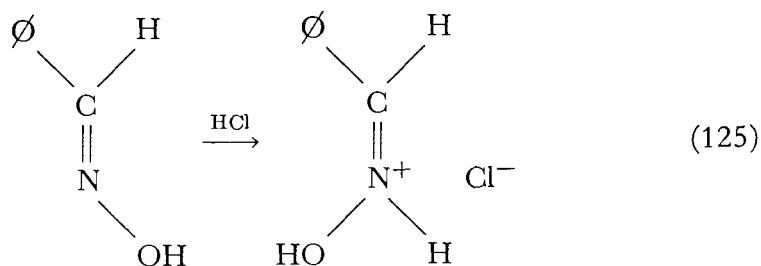
ever, may isomerize further to amides under the same conditions as they are formed^{136a} (Eq. 124). Some aliphatic nitrones have been reported



to undergo spontaneous dimerization.^{48b} N, α -Tetramethylenenitron (tetrahydropyridine N-oxide) and some related nitrones have been shown to trimerize so rapidly that the monomers could not be isolated^{32c}; on standing, the trimers slowly convert to crystalline dimers. Both trimers and dimers apparently have no new C—C bonds, and are believed

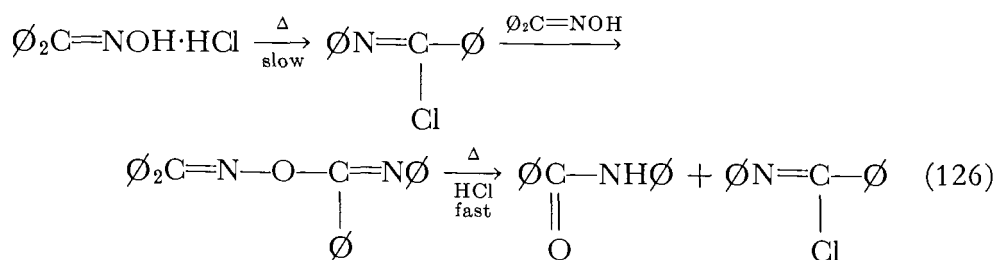
to be hexahydro-1,3,5-triazines and tetrahydro-1,4,2,5-dioxadiazines, respectively.

ACIDS Strong mineral acids convert oximes to salts, which are usually readily isolable. Isomerization to a different geometrical isomer often accompanies salt formation; this is particularly true of aldoximes, where the ordinarily stable *syn*-isomers react with hydrogen chloride to form the hydrochlorides of the *anti*-isomers^{117, 137} (Eq. 125). O-Alkyl oximes, which are too weakly basic to form stable salts, are nevertheless subject



to acid-catalyzed isomerization.¹¹⁷ Nitrones form salts readily, but isomerization has not been observed.

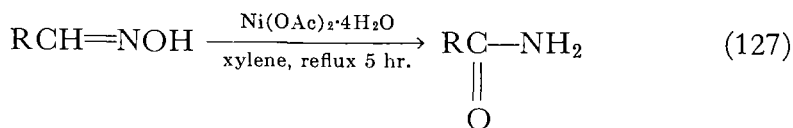
Oxime salts undergo the Beckmann rearrangement when heated. The most effective acids are those that would be capable of esterifying the oxime hydroxyl, such as sulfuric and polyphosphoric acids^{26b, 138a}; hydrochlorides rearrange reluctantly at first, and then go autocatalytically, owing to the formation of some imidoil chloride, which can esterify the hydroxyl group^{138b} (Eq. 126). Lewis acids, such as boron fluoride or aluminum chloride, also catalyze the Beckmann rearrangement; there is



reason to believe that the addition product with BF_3 attached to N must rearrange to that with BF_3 on O before the rearrangement step can take place.¹³⁹ A more extensive discussion of the Beckmann rearrangement is given ahead, in connection with acylation.

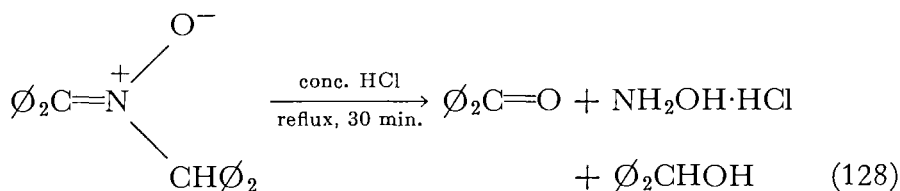
Aldoximes are converted to amides by warming with strong acids. Since aldoximes are very easily dehydrated to nitriles, it seems not unlikely that the amides arise from subsequent reaction of the nitrile with the wet acid. This may not be the case with isomerization catalyzed by nickel

acetate ¹⁴⁰ (Eq. 127), however; it is a useful method for compounds sensitive to acid elsewhere in the molecule.



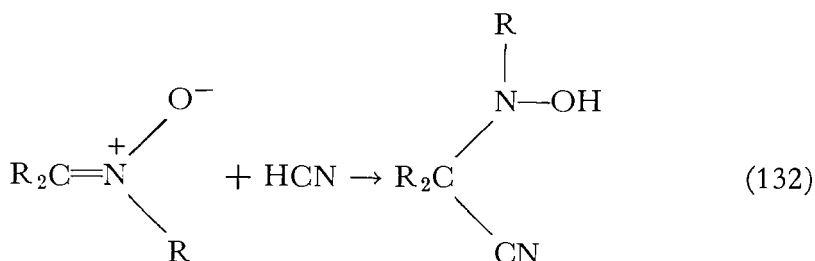
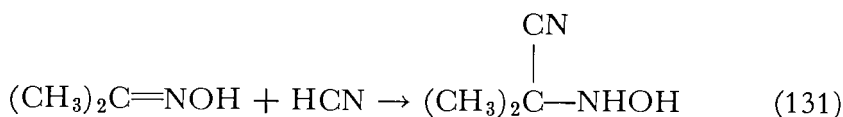
Aqueous acids slowly hydrolyze ketoximes and aldoximes to hydroxylamine and the parent carbonyl compound; refluxing hydrochloric acid usually accomplishes this fairly rapidly, but there are many exceptions.¹⁴¹ There is apparently a pH at which the rate will be a maximum; for acetoxime it is 2.3, and the rate falls to nearly zero at pH > 5.^{141b} O-Alkyl oximes are more resistant to hydrolysis and usually require prolonged refluxing or higher temperatures. Nitrones, on the other hand, are quite easily hydrolyzed, some of them in only a few minutes at room temperature,^{17d} so that their salts can only be handled with protection from moisture. Some N-benzyl and N-benzhydryl oximes have been observed to undergo rearrangement to the O-substituted isomers during acid-catalyzed hydrolysis; it is not clear whether this is due to especially easy thermal rearrangement, or to a separately acid-catalyzed reaction. Dealkylation may also occur, producing alcohol and hydroxylamine¹³⁵ (Eq. 128). Elimination of the N-substituent as olefin has been reported in one case.

Other methods for obtaining ketones or aldehydes from their oximes

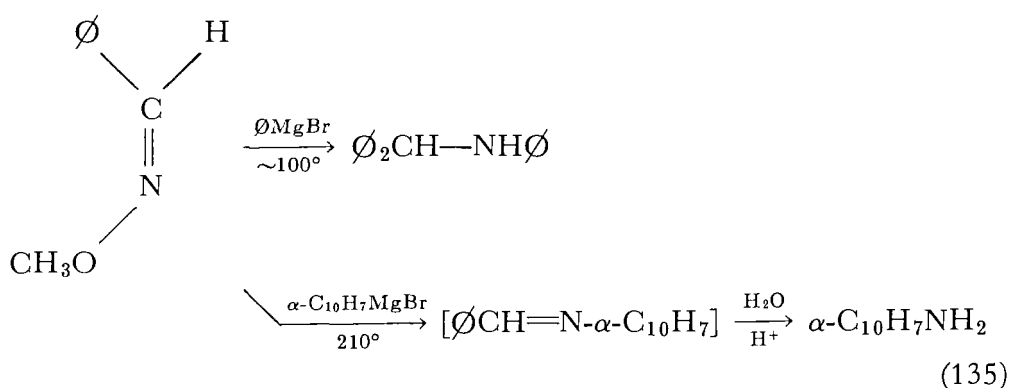
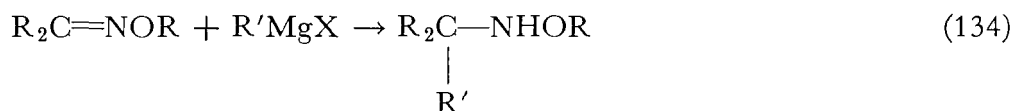
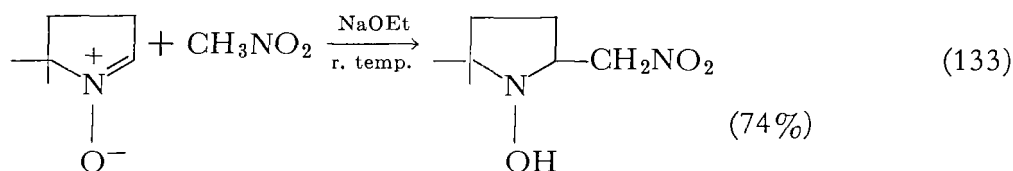


when hydrolysis is difficult include reaction with nitrous acid or sulfurous acid, and with formaldehyde¹⁴¹; these are discussed in the ensuing pages. Bases do not bring about hydrolysis of unsubstituted oximes, but form stable salts.

COMPLEXES Transition metal and related cations form complexes with oximes; the stability varies widely with both the cation and the structure of the oxime. The color reaction of some simple oximes with ferric chloride has already been cited. By far the most important complexes are those formed from α -dioximes, α -keto oximes, and *ortho*-hydroxy benzaldoximes, for they are chelate in structure, unusually stable, and uncharged, often soluble in organic solvents but not in water. Their

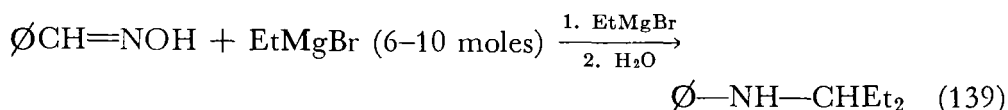


GRIGNARD REAGENTS Carbanions, such as those derived from nitroalkanes, add quite readily to nitrones^{48b} (Eq. 133); Grignard reagents behave similarly.^{48b, 149} Oximes and their O-alkyl derivatives also add Grignard reagents (Eq. 134), but the reaction has been observed to go further,¹⁵⁰ with replacement of the alkoxyl group in some cases (Eq. 135), and to lead to aziridine formation when α -hydrogens are present¹⁵¹ (Eq. 136). Salt formation, with destruction of one equivalent of Grig-



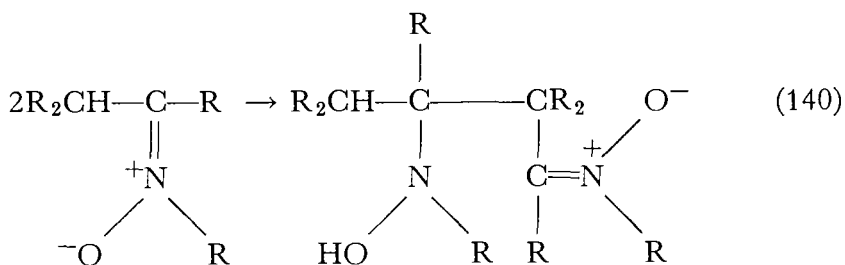
nard reagent, is apparently the first step; subsequent reaction requires forcing conditions. Since propiophenone oxime and methylmagnesium bromide give a product that is different from (but isomeric with) that from acetophenone oxime and ethylmagnesium bromide,¹⁵² it is evident that the second step is not simple addition of Grignard reagent across the

Benzaldoximes react with Grignard reagents in a way that is easiest to interpret as involving rearrangement (perhaps MgBr_2 -catalyzed Beckmann?) preceding addition; secondary amines are formed as the principal product ^{150a, 153b} (Eq. 139). It is true that formanilides give the same products when treated with Grignard reagents, there is also a precedent



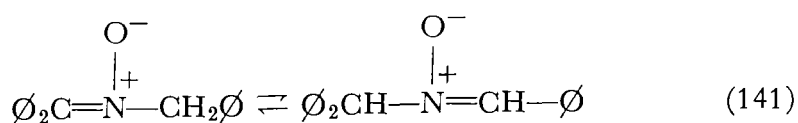
for reduction followed by rearrangement in the course of reaction of some oximes with lithium aluminum hydride (discussed ahead in connection with reduction).

Since nitrones add carbanions at the $\text{C}=\text{N}$ bond, one might reasonably expect them to add their own conjugate bases, under conditions where they can be formed. The result would be an analog of the aldol condensation, forming a β -hydroxylamino nitrone (Eq. 140). Such reactions take place very readily and are evidently in some part responsible for the instability of aliphatic nitrones, most of which cannot be prepared at all under even mildly basic conditions. ^{17d, 48b} The example of phenylhydroxylamine and acetone ^{17b} has been discussed in the section on Alkyl and Aryl Hydroxylamines. Those nitrones that do not condense spontaneously can be made to do so under catalysis by sodamide. ¹⁵⁴ A competing head-to-head dimerization has also been observed ^{136b} with certain aldonitrones.



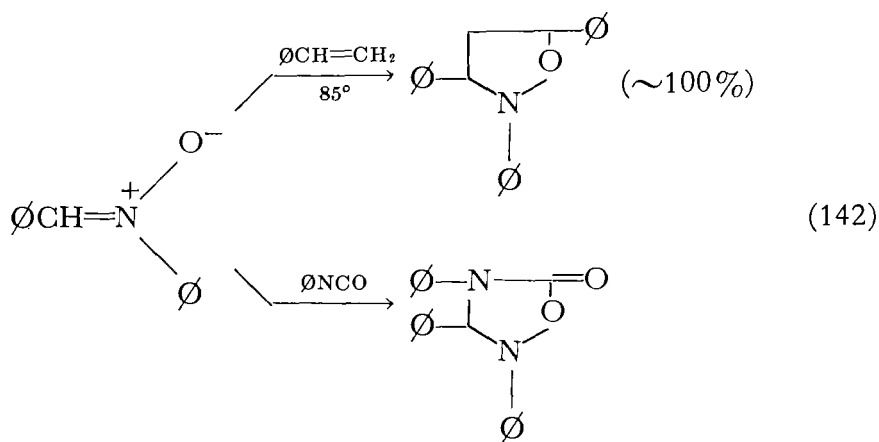
In the absence of competing reactions, base catalyzes a prototropic isomerization of nitrones; the structural requirements have not been adequately explored, but appear to include the presence of an activated α -hydrogen on the N-attached group, and derivation of the alkylidene moiety from a ketone or aldehyde having no α -hydrogens. Benzophenone N-benzylloxime is a representative example; it equilibrates slowly with benzaldehyde N-benzhydryloxime on treatment with base or on chromatography on certain adsorbents ^{121,135} (Eq. 141). The transformation ap-

pears to be definitely easier than the analogous 1,3-shift occurring with

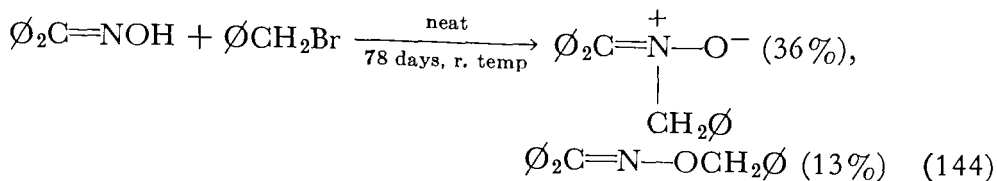
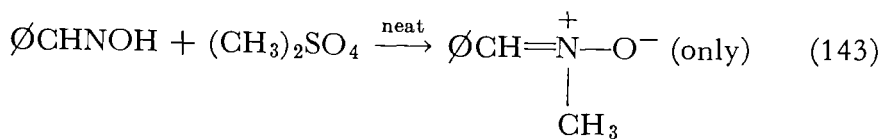


the corresponding imines (Chapter 7); it is sometimes known as the Behrend rearrangement.

1,3-CYCLOADDITIONS Nitrones, but apparently not oximes or O-alkyl oximes, can undergo 1,3-cycloaddition with $\text{C}=\text{C}$ or $\text{C}=\text{N}$ unsaturation^{17b, 33, 155}; five-membered rings, isoxazolidines^{33, 156} or 1,2,4-oxadiazolidines, are formed (Eq. 142).

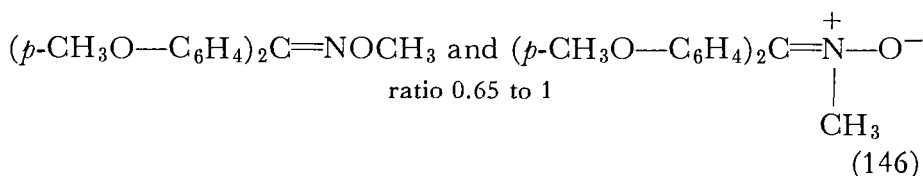
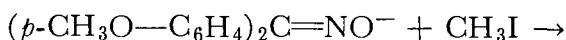
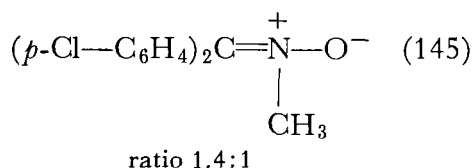
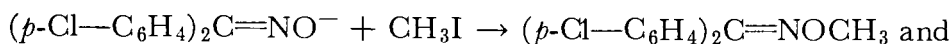


ALKYLATION Oximes, being very weak bases, are not unexpectedly rather poor nucleophiles and react in the un-ionized state only with the most active alkylating agents, such as methyl sulfate. Substitution is then predominantly or exclusively on the nitrogen, producing nitrones^{121, 117} (Eqs. 143, 144). The alkylation of oxime anions occurs much



more easily, and invariably gives mixtures, in which the O-substituted isomer usually predominates^{121a}. Oxime anions can in principle be

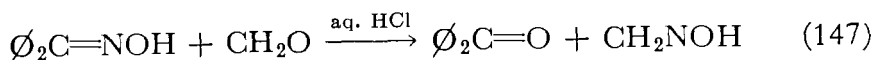
expected to manifest their nucleophilic activity at three different sites: at C, to yield nitroso compounds; at N, to yield nitrones; and at O, to yield O-alkyl oximes. The first of these has not yet been observed, and the factors that determine the relative rates of attack at O and at N have been only incompletely investigated.^{121a} Although oxime anions are ambident anions, the factors governing the site of alkylation are not in all ways the same as those that have been established for other types of ambident anions, such as phenoxides. The reactions are ordinarily second order. Electron withdrawal in the alkylidene moiety retards N-substitution^{117, 121a} (Eqs. 145, 146). The influence of electronic effects



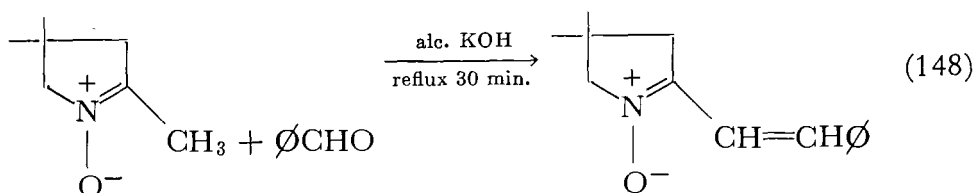
in the alkylating agent and of the nature of the leaving group are small, but bulk in the alkylating agent may be important, inasmuch as methylation produces markedly more nitrone than does benzylation,^{121a} and triphenylmethyl chloride produces only O-substitution.¹³⁵ The process of alkylation does not of itself cause geometrical inversion with those oximes capable of geometrical isomerism; the *p*-nitrobenzophenone oximes and the nitrones derived from them have been unequivocally related,¹²⁴ for example. *syn*-Aldoximes give mostly O-methyl derivatives, whereas *anti*-aldoximes give a much higher proportion of nitrone¹¹⁷; curiously, although the O-methyl oximes produced from the isomeric aldoximes are distinct, the same nitrone (configuration uncertain) is produced from each. Alkylation of the silver salts of oximes gives very largely O-alkylation.¹¹⁷ Further alkylation has not been observed with O-alkyl oximes, but alkylation of nitrones to alkoximmonium salts has been observed with powerful alkylating agents (e.g., $\text{Et}_3\text{O}^+\text{BF}_4^-$).

CARBONYL COMPOUNDS Oximes react with aldehydes and ketones under solvolytic conditions in such a way as to accomplish hydroxylamine exchange. With formaldehyde, the exchange is particularly rapid,¹⁴¹

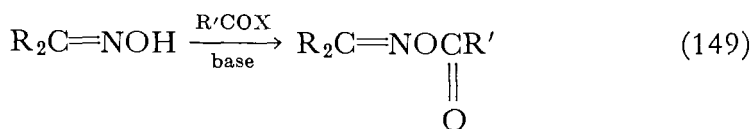
and the equilibrium appears to be in favor of formaldoxime (Eq. 147). As a result, other ketones and aldehydes can be released from their oximes much more readily than by simple hydrolysis, by treatment with formaldehyde and acid. Reaction of a different type, which has been



observed only with certain cyclic nitrones, where the inclusion of the nitrone function in a ring renders it less subject to cleavage, is base-catalyzed condensation with an active methylene position (Eq. 148).^{48b}

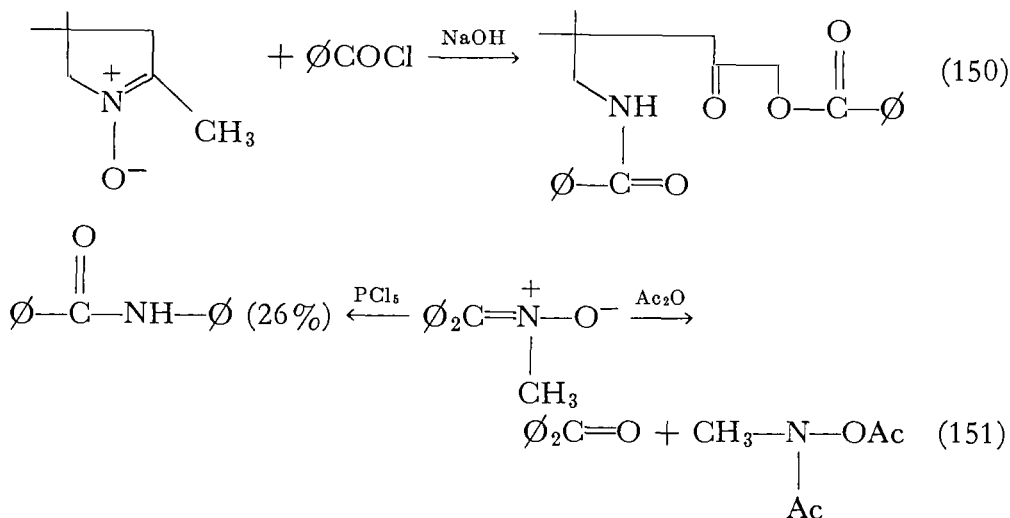


ACYLATING AGENTS Acylating agents react with oximes to yield monoacyl derivatives, which can usually be isolated readily so long as the acyl group is not derived from a very strong acid (Eq. 149). Not only acetyl, but picryl and even toluenesulfonyl derivatives have been made; the latter are generally very unstable and deflagrate upon being brought to room temperature. The evidence is completely convincing that the compounds are O-acyl derivatives.^{59, 157} N-Acyl oximes are not known, and reactions besides direct acylation that should lead to them have always given only the O-acyl isomer, circumstances that suggest that N-acyl oximes are unstable toward rearrangement to the O-acyl structure. Geometrically isomeric oximes yield isomeric acyl derivatives, which can

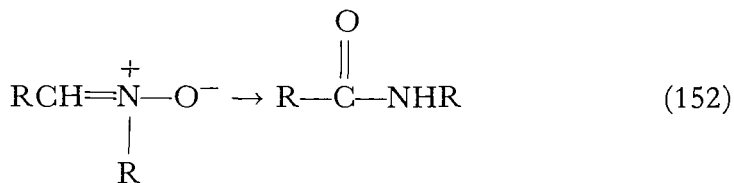


be hydrolyzed back to the original oxime by mild aqueous base. O-Substituted oximes are inert to acylation, but nitrones have been reported^{48b} to react in a way reminiscent of the Polonovski reaction of pyridine N-oxides (which can actually be considered as nitrones, too). An acyloxy group becomes attached to an adjacent carbon, and the nitrogen is reduced to the amide state (Eq. 150). Benzophenone N-methyloxime gives benzanilide, the product of Beckmann rearrangement with dealkylation, in low yield when treated with phosphorus pentachloride; no N-methylbenzanilide is formed.⁵⁹ With acetic anhydride, no rearrange-

ment takes place, but the nitron is cleaved to benzophenone (Eq. 151). Aldonitrones are converted to secondary amides by acylating agents, but



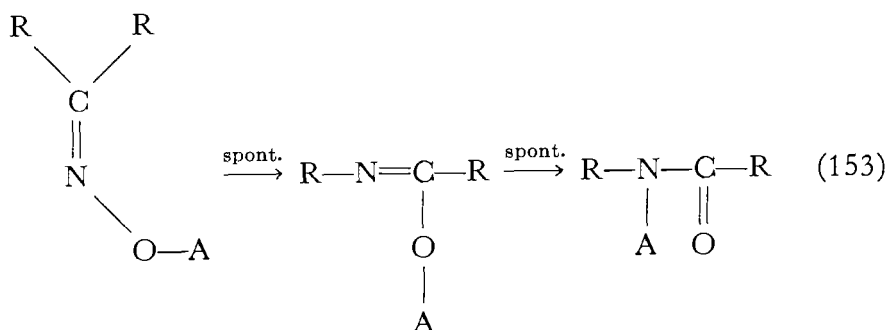
oxygen migration, not Beckmann rearrangement, is involved ¹⁵⁸ (Eq. 152).



Under more strenuous conditions, and especially with derivatives of strong acids, acylation of oximes may bring about Beckmann rearrangement,^{26b, 127} fragmentation,¹⁵⁹ dehydration to nitriles,¹²² aromatizing dehydration (Semmler-Wolff aromatization),¹⁶⁰ or cyclodehydration.¹⁶¹ Since all these reactions appear to stem from initial O-acylation, it is convenient to take them up in terms of the reactions of O-acyl oximes.

O-ACYL OXIMES; BECKMANN REARRANGEMENT The Beckmann rearrangement was originally looked upon as a catalyzed isomerization of an oxime to an amide. O-Alkyl oximes are inert, and nitrones rearrange only with concomitant dealkylation, if at all.⁵⁹ The "catalysts" first used, sulfuric acid or phosphorus pentachloride, did not lend themselves to isolation of intermediates. Our present understanding of the role of O-acyl derivatives in the Beckmann rearrangement is in large part due to the researches of Kuhara with O-benzenesulfonyl oximes and of Chapman with O-picryl oximes.¹⁶² They showed that these O-acyl oximes rearrange readily in the dark and without any catalyst; the initial products, O-acyl imidic acid derivatives, themselves undergo further

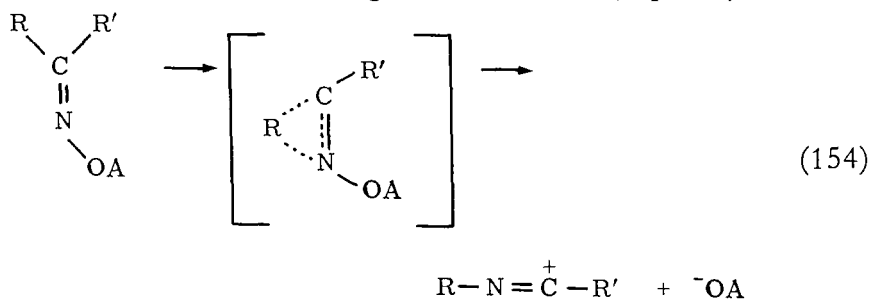
rearrangement involving a 1,3 O-to-N shift of the acyl group (Eq. 153). The first stage is the slow one, and follows first-order kinetics, with a



(Beckmann rearrangement)

velocity proportional to the ionizing power of the medium. If water is present, the acyl group is usually lost hydrolytically, giving a monosubstituted amide.

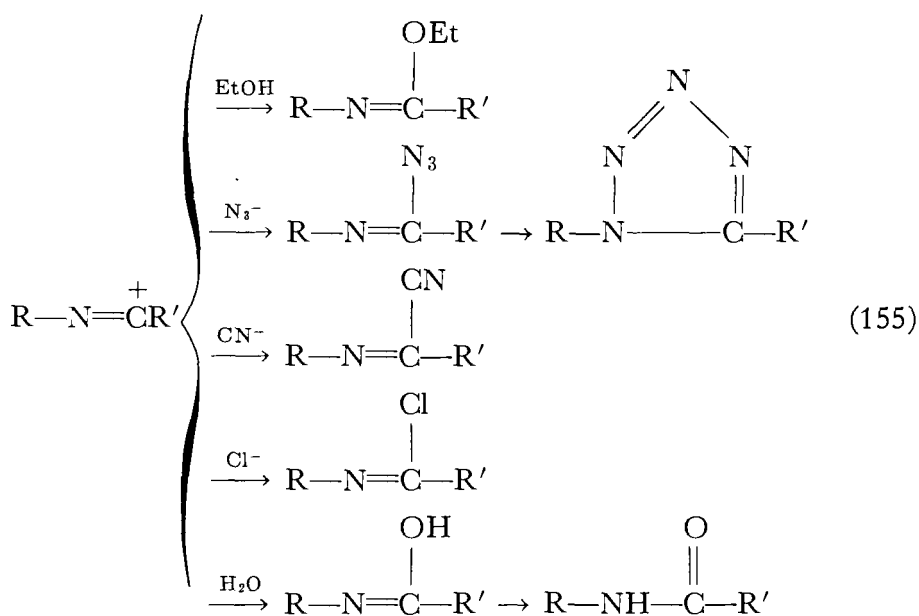
The Beckmann rearrangement was observed early to be stereospecific with respect to stereoisomerism in oximes of unsymmetrical ketones; the group that migrates to nitrogen is determined largely by the configuration of the oxime, so long as equilibrating conditions are not used. The controversy over the assignment of the proper configuration to isomeric oximes has been mentioned earlier in this section; when it was finally resolved, it was seen that it is the group *anti* to the oxime oxygen that migrates. It was also established in various ways that the migrating group never becomes detached from the molecule, and that its configuration is retained if its point of attachment is an asymmetric carbon. The evidence supporting these general conclusions is considerable.^{26b, 127} Taken as a whole, it leads to the concept that the Beckmann rearrangement is an ionization accompanied by migration of the *anti* substituent from C to N through a quasi-three-membered-ring transition state (Eq. 154).



The ease with which the process takes place would obviously be dependent on the stability of the anion that is generated, AO^- , and on the ability of the migrating group to assist in stabilizing the growing positive charge. These consequences are adequately borne out by the facts that rearrangement occurs fastest with those acyl derivatives that produce an

anion of a very strong acid, and with those in which the migrating group carries strongly electron-donating substitution. The electronic requirements of R and A in the mechanistic formulation are thus the reverse of each other.

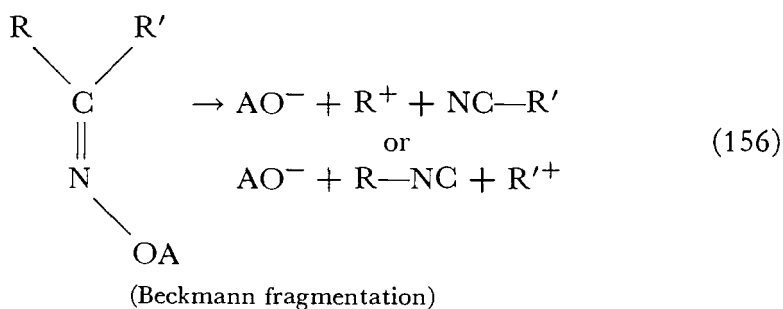
The cation $R-N=CR'^+$ (or $R-N^+=CR'$) can be intercepted by carrying out the rearrangement in the presence of various nucleophiles, which do not need to be strong. In the presence of alcohols, it reacts to form imidate esters; in the presence of azide ion, to form imidoazides that cyclize spontaneously to tetrazoles; in the presence of cyanides, to form α -imino nitriles, and in the presence of chloride, to form imidochlorides (Eq. 155).



The most widely used reagents for direct accomplishment of the Beckmann rearrangement are sulfuric acid, polyphosphoric acid, and phosphorus pentachloride. Although unrearranged acyl oximes derived from them have not been isolated as intermediates, each is believed to form them, respectively, by sulfonation, phosphorylation, and chlorophosphorylation. Oxime-O-sulfonic acids have actually been prepared in a different way, reaction of ketones with hydroxylamine-O-sulfonic acid, and found to rearrange as expected. Differences in which group migrates in unsymmetrical ketoximes have been encountered among these and other reagents that bring about the Beckmann rearrangement. The usual case is that stereochemically pure oximes give single, pure amides when phosphorus pentachloride is the reagent, but the strongly acidic reagents, particularly sulfuric acid, occasionally give mixtures of amide isomers. This is almost certainly due principally to acid-catalyzed equi-

bration of the *syn*- and *anti*-forms of the oxime before rearrangement. If such interconversion should be very fast compared to the rearrangement step, the ratio of isomeric amides in the product would be determined by the relative intrinsic rates of migration of the two groups involved.¹⁶³ As a practical matter, the amide obtained in largest amount by the process of oximation of an unsymmetrical ketone followed by Beckmann rearrangement is nearly always the one with the bulkiest group attached to nitrogen in the case of aliphatic systems; this is apparently due to the operation of relative migration aptitudes. With benzophenones, on the other hand, the electronic effect of *para* substituents is almost without influence; the products are largely determined by the stereochemistry, and a nearly 1:1 ratio of isomeric amides is obtained.¹⁶³

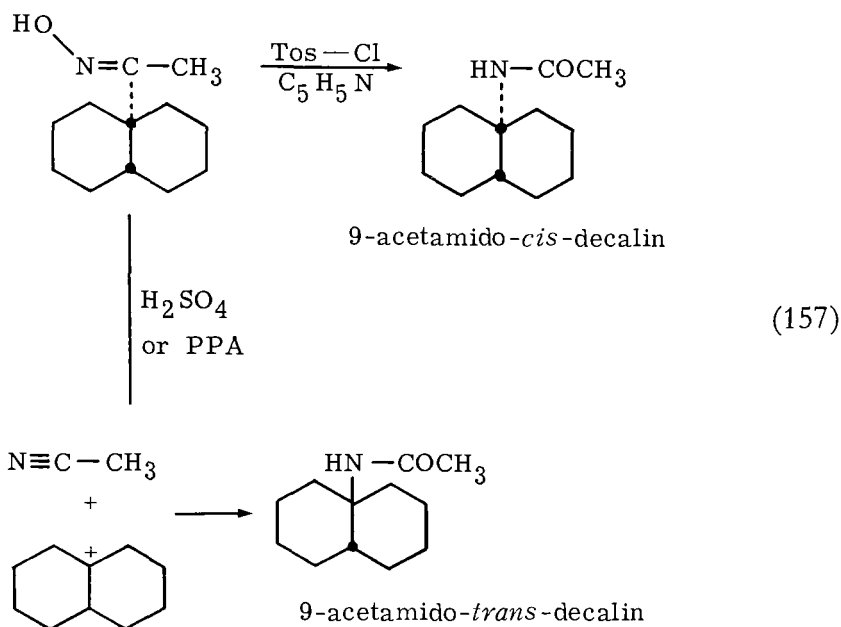
BECKMANN FRAGMENTATION Fragmentation of O-acyl oximes involves separation into the anion of the O-acyl group, one of the groups of the original ketone as a cation, and the remainder as a nitrile or isocyanide (Eq. 156). It only occurs with those compounds in which one group has exceptional stability as a cation and occurs most readily when the departing ionic fragments are *trans* to one another. Otherwise, the energetics



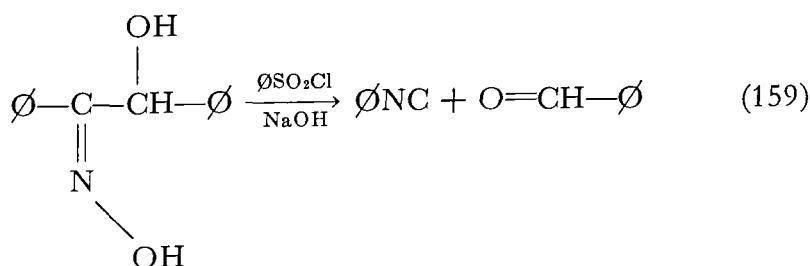
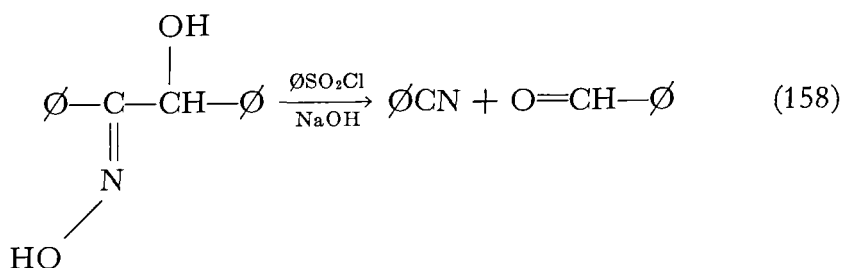
are evidently unfavorable, and normal Beckmann rearrangement occurs. The required stability of the cation is provided if one group is tertiary alkyl, α -hydroxy alkyl, acyl, etc.¹⁵⁹ The products actually isolated, as well as the very occurrence of fragmentation, depend in addition on the reaction medium, for the cations must stabilize themselves by combination with a nucleophile, or ejection of a proton to become an olefin. If no better course is available, the cation is likely to combine with the nitrile

to form the usual rearrangement intermediate, $\text{R}-\overset{+}{\text{C}}=\text{N}-\text{R}'$ (Ritter reaction, see Chapter 5). The products are then the same as though no fragmentation had occurred, except that the group found attached to nitrogen will have been racemized if its point of attachment is an asymmetric carbon.¹⁶⁴ 9-Acetyl-*cis*-decalin oxime, for example, gives 9-acetamido-*cis*-decalin, the unracemized product of normal Beckmann rearrangement, when rearranged through formation of its tosyl derivative in pyridine, but with concentrated sulfuric acid or polyphosphoric acid as

the rearranging agent, the product is 9-acetamido-*trans*-decalin, the configuration of lower energy (Eq. 157). Evidently, in the latter two reagents, fragmentation and recombination occurred (the *cis*-isomer was shown to be stable to conversion to the *trans*-isomer under the latter reaction conditions).

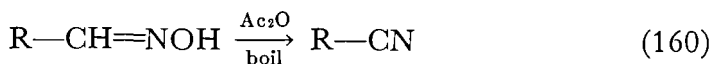


Fragmentation may show stereochemical specificity; the isomeric benzoin oximes give different products, for example.¹⁶⁵ Each isomer gives benzaldehyde (formed from the cation $\text{C}_6\text{H}_5\text{CHOH}^+$), but the *syn*-phenyl isomer gives benzonitrile as the other product, while the *anti*-phenyl isomer gives phenyl isocyanide (Eqs. 158, 159). It is evident that

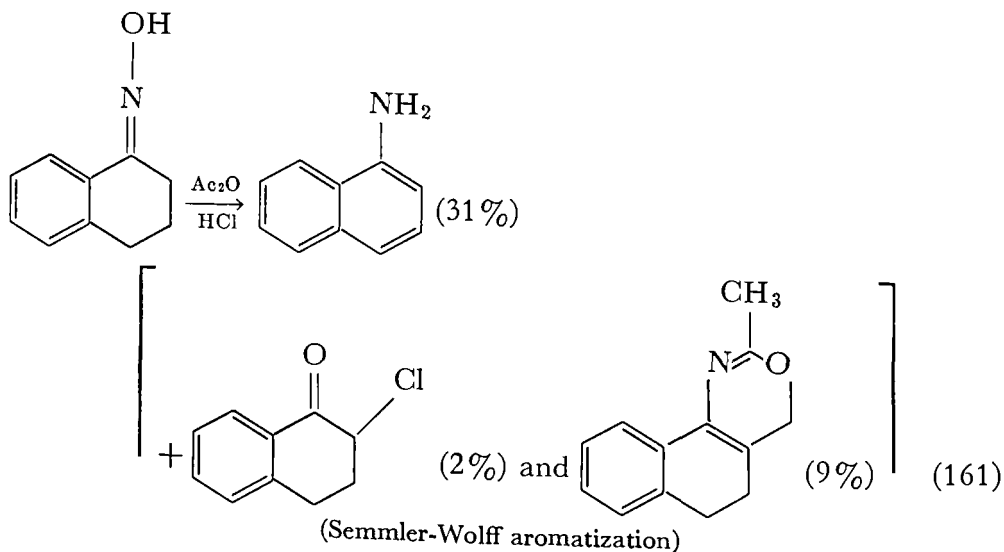


the formation of phenyl isocyanide involves actual migration of a group from C to N; the transition state must therefore be very similar to that for normal Beckmann rearrangement, if, indeed, completed rearrangement does not precede fragmentation. The reactions that give rise to nitriles on the other hand, do not necessarily involve even partial C—to—N migration before fragmentation occurs. The relationship of the fragmentations that produce isocyanides to the Passerini reaction (Chapter 5), which is essentially the reverse process, is worth noting.

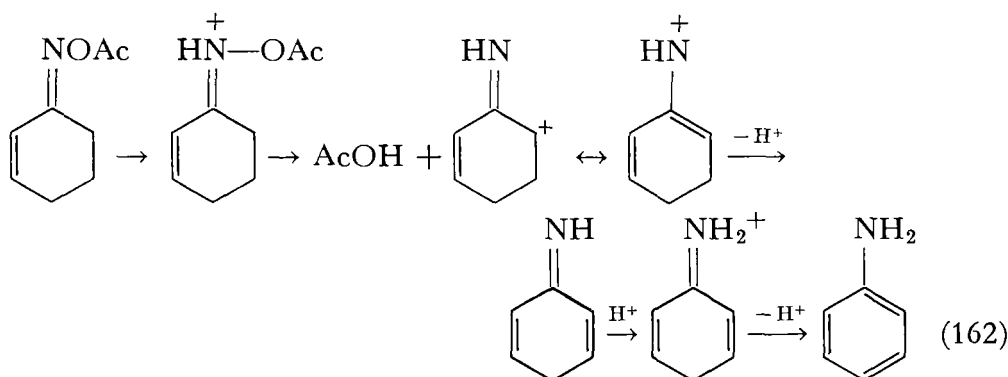
Aldoximes readily undergo dehydration to nitriles through O-acyl derivatives. The *syn*-O-acyl isomers are hydrolyzed by dilute base back to the original oxime, but the *anti*-isomers undergo a base-catalyzed elimination that is essentially a fragmentation in which the electrophilic product is H^+ combined with the attacking base. From the preference of this reaction for the *anti* configuration, it can be seen to be a member of the general class of *trans* eliminations.^{122, 166} When acylation is conducted under less mild conditions, and particularly by heating with acetic anhydride,¹⁶⁷ dehydration to nitrile takes place directly, regardless of the geometrical configuration (Eq. 160). Various other reagents have been used to dehydrate oximes more or less successfully.¹⁶⁸



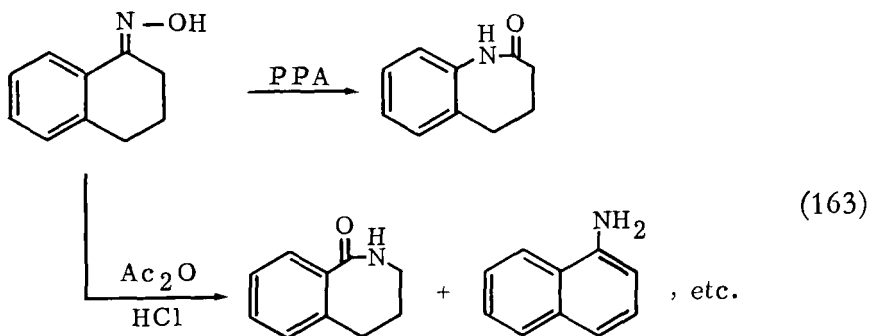
SEMMLER-WOLFF AROMATIZATION Oximes of cyclohexenones and related heterocyclic ketones, such as 3-ketodihydrothiophene, undergo a multistep dehydration to form aromatic amines when treated with acylating agents and strong acid. This reaction is known as the Semmler-Wolff aromatization,¹⁶⁰ and is commonly brought about with "Beckmann's mixture," a solution of hydrogen chloride in acetic anhydride and glacial acetic acid (Eq. 161). It is always competitive with the



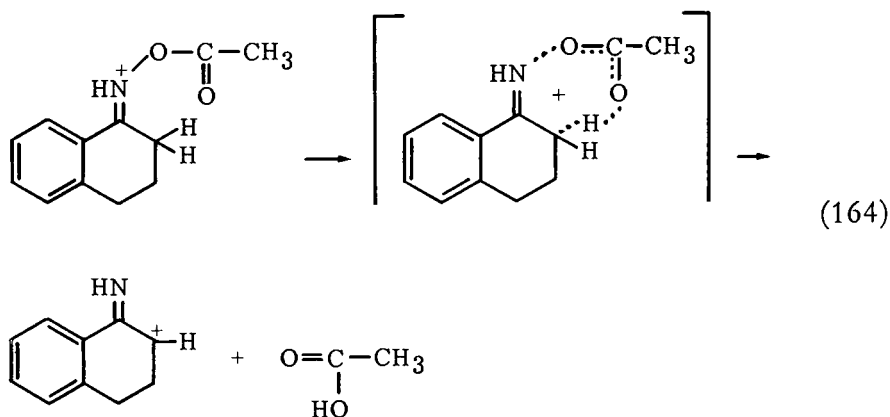
Beckmann rearrangement; unfortunately, yields are usually low and seldom better than moderate. It is sometimes encountered as a side reaction when the Beckmann rearrangement is attempted with other reagents. The mechanism¹⁶⁹ that seems most plausible assumes that acetylation of the oxime is the first step, followed by protonation and elimination of acetic acid to produce an aza-allylic cation, which can stabilize itself as an aromatic amine by a series of allylic shifts brought about by deprotonation and reprotonation (Eq. 162). The observed by-products can be readily explained as arising from the proposed intermediates.



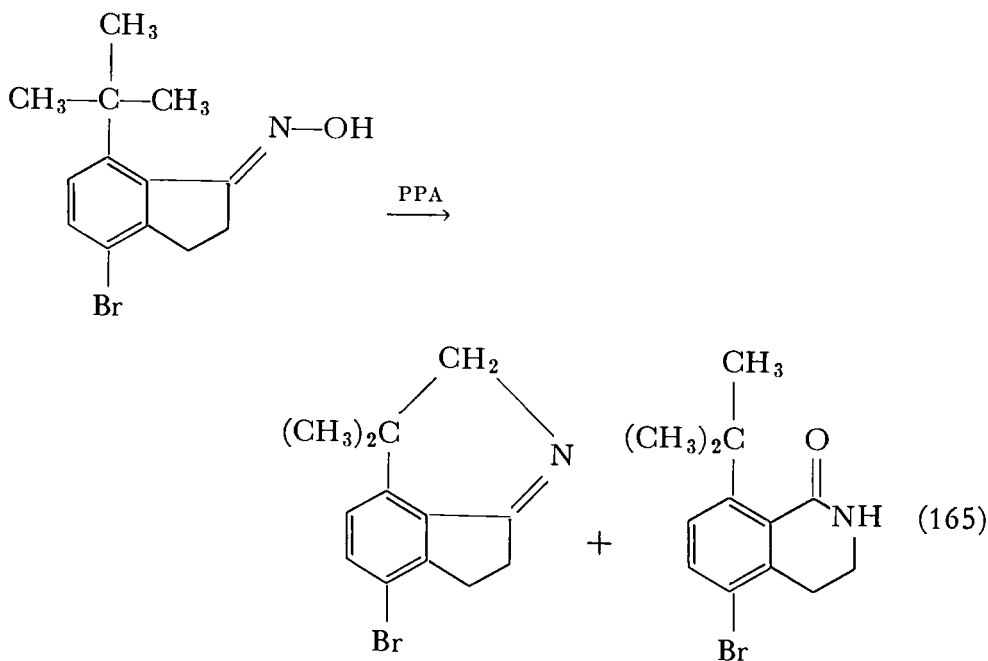
The question of how the initial elimination of acetic acid takes place in the Semmler-Wolff aromatization is related to the behavior of the oximes when they undergo the Beckmann rearrangement. With several α -tetralone oximes, it has been observed that the Beckmann rearrangement initiated by reagents that do not interconvert the isomers gives lactams derived from migration of the aryl group¹⁶⁰; the oximes are thus in the *anti*-aryl configuration. When the Semmler-Wolff aromatization is carried out with Beckmann's mixture, however, the small amount of accompanying lactam is derived from alkyl migration; the oxime has evidently been transposed to the *syn*-aryl configuration (Eq. 163). This is perhaps adequately explained by the fact that the relative rates of Beckmann rearrangement of *syn*- and *anti*- α -tetralone oximes (> 300 for



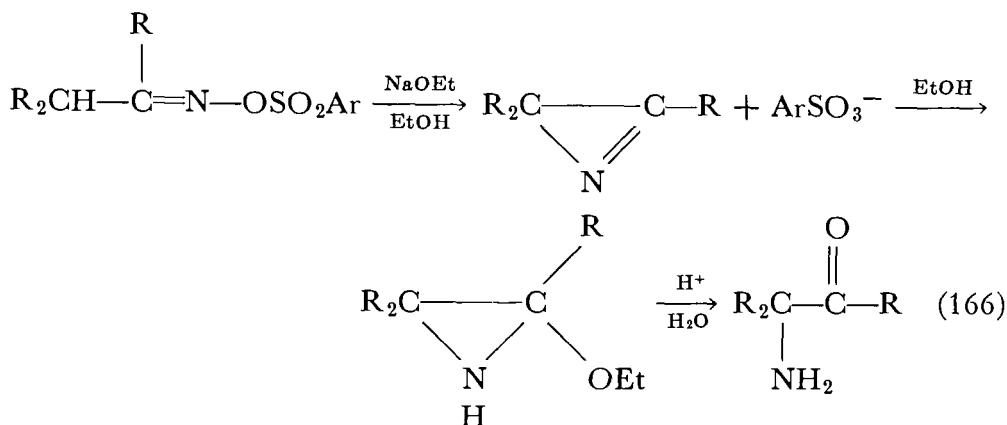
the O-picryl derivatives)¹⁷⁰ strongly favor alkyl migration when both routes are available as a result of geometrical equilibration. It is thus not inconsistent for acetic acid to be eliminated by a cyclic process from the *anti*-isomer (Eq. 164) at the same time as the Beckmann rearrangement is taking place through the *syn*-isomer, although *trans* elimination is also reasonable.



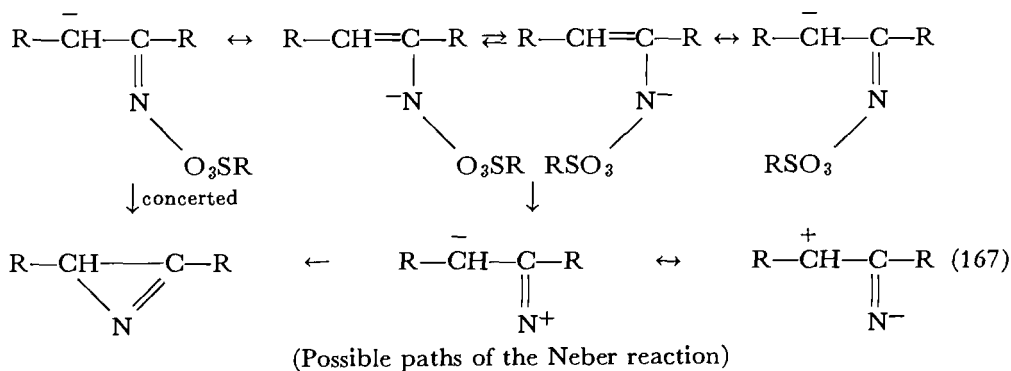
Two distinct kinds of cyclodehydration of oximes have been observed. In one, a six-membered ring is formed by closure to a saturated carbon atom, in an oxime in which Beckmann rearrangement is strongly inhibited by steric factors¹⁶¹ (Eq. 165). The reaction has been pictured as an insertion reaction of an electron-deficient cationic nitrogen intermediate. The other type of cyclodehydration takes place on treatment of O-sulfonyl



oximes with strong base, and gives rise to azirines¹⁷¹ by ring closure to an α -carbon; it is known as the Neber reaction (Eq. 166).¹⁷²

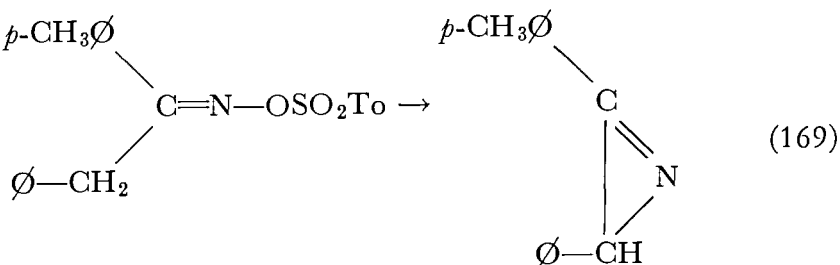
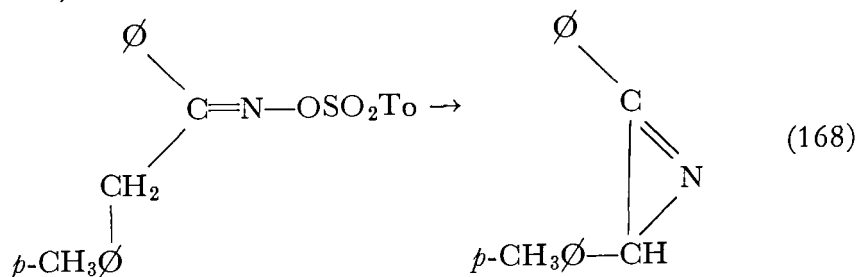


The usual experimental result of the Neber reaction is the isolation of further transformation products of the azirines, for they are reactive substances whose ring is easily opened; α -amino ketones or their acetals are the usual products.¹⁷² The direction of cyclization is independent of the geometrical configuration of the oxime and appears to involve the most acidic α -hydrogen.¹⁷³ There is little question but that the first step is removal of a proton from an α -position; whether separation of sulfonate ion occurs prior to ring closure or in concert with it is not yet established, and, indeed, may depend on both the reaction conditions and the structure of each sulfonyl oxime (Eq. 167). The lack of stereospecificity is consistent with either path, for generation of an anion at the α -position should promote geometrical equilibration, and if subsequent reaction is fast relative to reprotonation, the observed stereochemical control of the

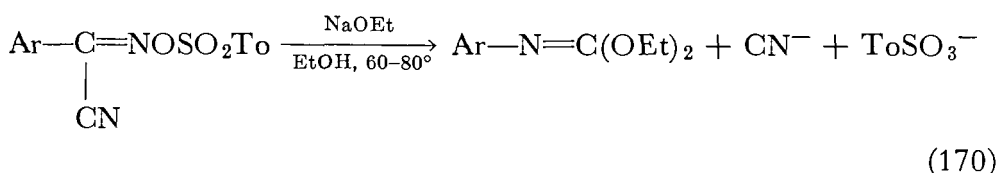


competing Beckmann rearrangement would not be disturbed. The possibility that the azirines might interconvert tautomerically or be formed through an intermediate symmetrical about the α -carbon and the azomethine carbon is precluded by the fact that a pair of isomeric arylaceto-

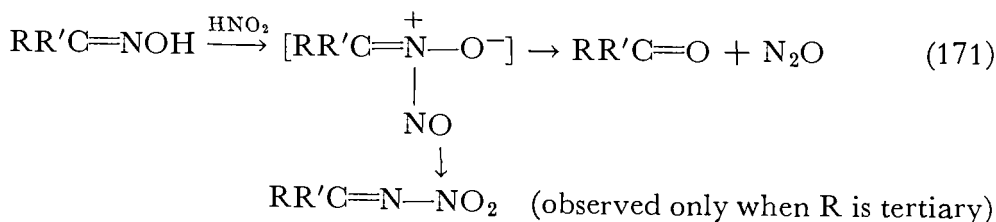
phenone oximes have been found to give entirely distinct products¹⁷⁴ (Eqs. 168, 169).



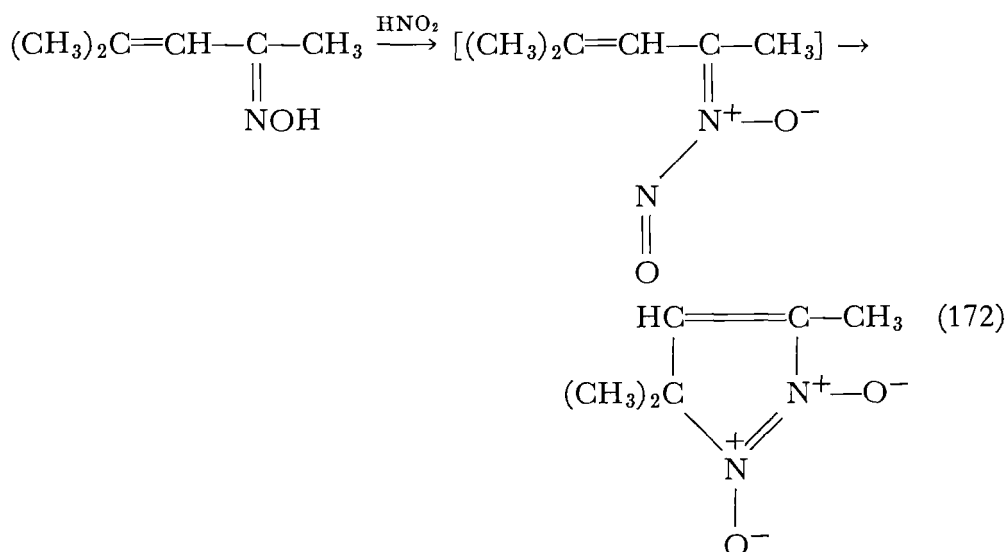
Three different consequences of treating O-acyl oximes with base have so far been mentioned: hydrolysis to the oxime, elimination to form nitriles, and the Neber reaction. One more type of reaction has been reported, in the special case of the oximes of aryglyoxylonitriles.¹⁷⁵ The O-tosyl derivatives are remarkable in that they do not undergo Beckmann rearrangement even at steam-bath temperatures. In warm, alcoholic alkali or ethoxide, both rearrangement and solvolysis of the cyano group occur, giving N-aryliminocarbonate esters in moderate to good yields (Eq. 170). The process is believed to be initiated by attack of ethoxide at the oxime carbon.



NITROSATING AGENTS Nitrosation of oximes, as of most other functions, differs markedly from ordinary acylation; neither O-acyl derivatives nor Beckmann rearrangement products are formed. The most general reaction is slow conversion to the parent ketone with release of nitrous oxide¹⁷⁶ (Eq. 171); it has been shown in the case of biacetyl monoxime that the

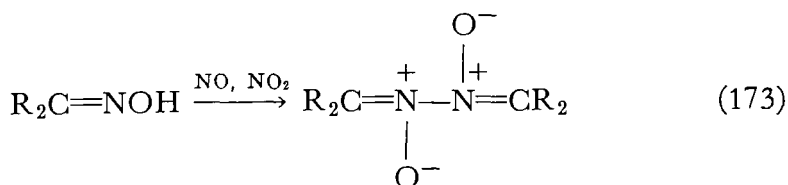


carbonyl oxygen derives from the oxime rather than from the nitrosating agent.^{176c} If one substituent on the oxime carbon is tertiary, a competing reaction leading to a nitrimine may become important.¹⁷⁷ The two reactions are believed to arise from a common N-nitroso nitron intermediate, which, incidentally, is also believed to be the precursor of the nitrimines formed from azine N,N'-dioxides and nitric oxide (see Chapter 11). The most convincing evidence for such an intermediate is the formation of a pyrazolenine 1,2-dioxide from the oxime of mesityl oxide, presumably by cyclization of the intermediate (Eq. 172). Pseudonitroles have been obtained in some instances¹⁷⁸; they are perhaps the result of

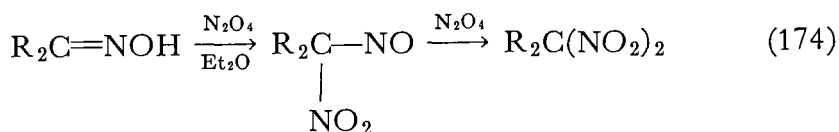


the action of oxides of nitrogen formed by the decomposition of nitrous acid (see ahead).

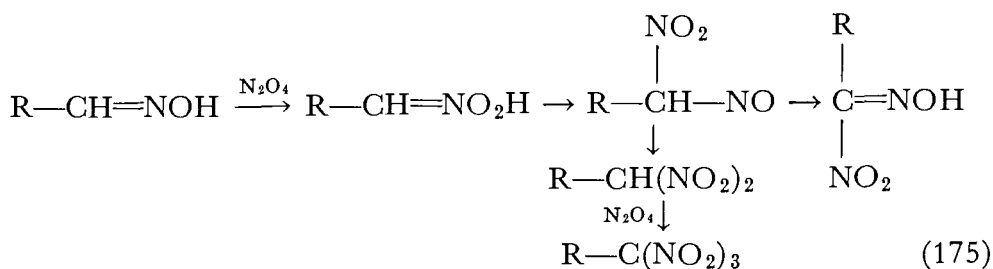
Nitrosyl chloride acts in a complicated way as either an oxidizing or a halogenating agent.^{176a, 179} Nitrous anhydride (actually, a mixture of nitric oxide and nitrogen dioxide) converts oximes to azine N,N'-dioxides¹⁸⁰ (Eq. 173).



Dinitrogen tetroxide reacts with ketoximes to form either pseudonitroles or their oxidation products, *gem*-dinitro compounds (Eq. 174)



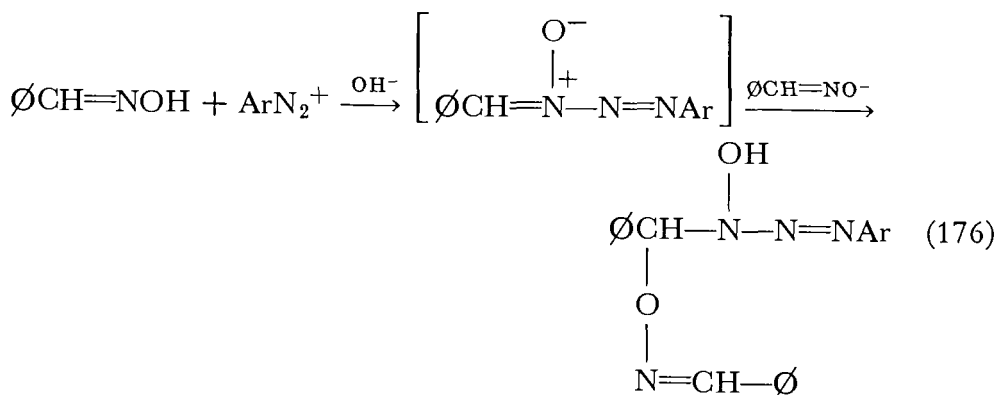
in moderate yields; this is known as the Ponzio reaction.^{178b, 181} Aldoximes also undergo these reactions, but the initial step, oxidation to a nitronic acid, has also been observed separately at temperatures below 0° (Eq. 175).¹⁸² At the same time, oxidation of the pseudonitrole must



compete with tautomerization to a nitrolic acid. Furthermore, other oxidation products (furoxans, azine dioxides) may be formed in minor amounts, as well as regenerated aldehyde, and continued exposure to excess reagent gives rise eventually to 1,1,1-trinitro compounds, often in substantial amounts (cf. Chapter 14).

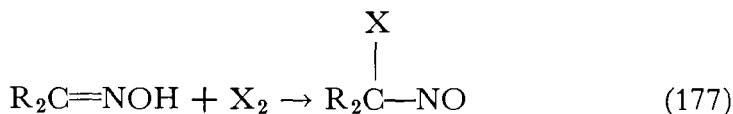
Salts of oximes react readily with nitric oxide; aldoximes are thus converted to a mixture of N-nitroso hydroxyamidoxime, $\text{R}-\text{C}(=\text{NOH})\cdot\text{N}_2\text{O}_2^-\text{Na}^+$, and a compound tentatively identified as a *gem-bis*(nitrosohydroxylamine),^{180b} $\text{R}-\text{CH}(\text{N}_2\text{O}_2\text{Na})_2$.

DIAZONIUM COUPLING Diazonium compounds in basic solution behave as electrophilic agents toward oximes and attack the nitrogen; the triazene N-oxides presumably initially formed are apparently themselves strongly electrophilic, for the products actually isolated are the result of reaction with a second molecule of oxime, which is substituted at oxygen by the original trigonal carbon^{183a} (Eq. 176). In the presence of copper compounds, however, the aldehyde hydrogen may become substituted

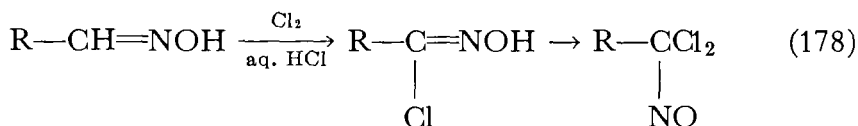


by aryl,^{183b} in what may be a free-radical reaction. Ketoximes, or, from formaldoxime, benzaldoximes are produced, in yields high enough to be of preparative value for aldehyde synthesis.

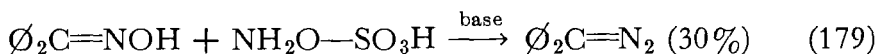
HALOGENATION Although most electrophilic agents attack oximes at O or N, halogens attack the trigonal oxime carbon, producing geminal halonitroso compounds^{179, 184} (Eq. 177). It is not known whether initial attack on O or N may actually occur, followed by a 1,3 or 1,2 shift of halogen. Nitrosyl chloride has been reported to give the same result.¹⁷⁹ Since the nitroso compounds produced have an intense, easily recognizable, blue color, this reaction has been recommended¹⁷⁹ as a qualitative test for oximes. Aldoximes are chlorinated further, forming 1,1-dichloro-



1-nitroso compounds, although it is quite possible to stop the reaction at the hydroximoyl chloride stage¹⁸⁵ (Eq. 178).

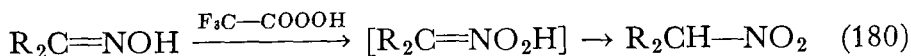


FORSTER REACTION The reaction of chloramine or hydroxylamine-O-sulfonic acid with oximes in alkaline solution has also been interpreted as electrophilic attack.¹⁸⁶ Diazoalkanes are produced in moderate yield (Eq. 179); if chloramine is used, it is not necessary to isolate it, for it may



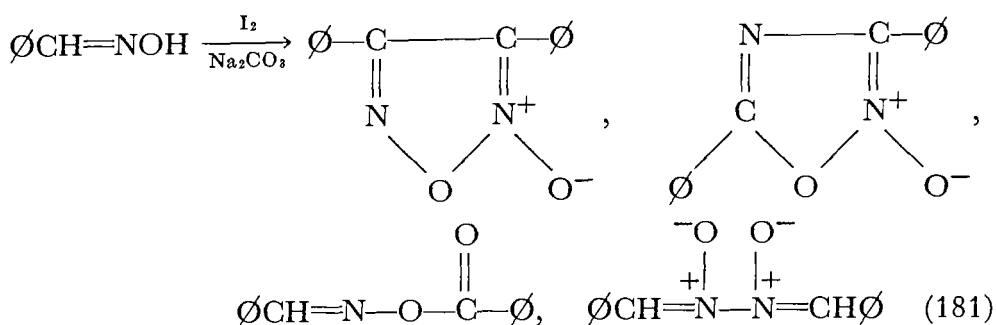
be generated *in situ* by treating the oxime with sodium hypochlorite and excess ammonium hydroxide. The reaction has not been thoroughly studied, but it does not seem unreasonable to suppose that electrophilic attack by NH_2-X occurs on both O and N, analogous to alkylation, and that only N-substitution leads to diazoalkane.

OXIDATION Oximes are not nearly so readily oxidized as hydroxylamines, and do not usually reduce Fehling's or Tollens' reagents unless they are first hydrolyzed. Stronger reagents bring about a variety of reactions, however. Peroxytrifluoroacetic acid converts ketoximes to mononitroalkanes¹⁸⁷ (Eq. 180), presumably through the *aci*-nitro structure. The reaction with N_2O_4 ,¹⁸² which has been mentioned under "nitrosation," is another example.

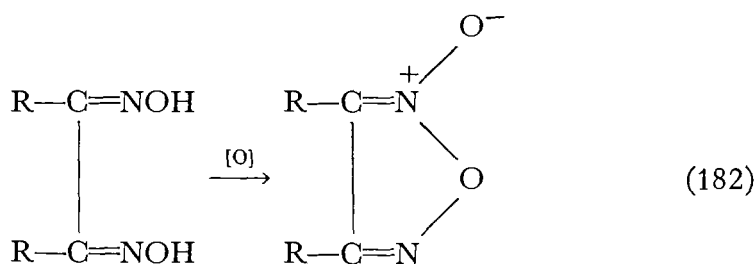


Ceric nitrate oxidizes oximes to iminoxy radicals (alkylidene nitroxides, $\text{R}_2\text{C}=\text{NO}\cdot$), which have been detected by electron-spin resonance although not yet isolated.¹⁸⁸

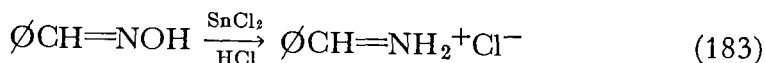
Other oxidizing agents, such as alkaline ferricyanide, have been shown to produce an interesting class of compounds, the azine N,N'-dioxides¹⁸⁰ (Eq. 173). The same substance is produced, along with furoxans, 1,2,4-oxadiazole 2-N-oxides, and O-acyl oximes, by oxidation with iodine¹⁸⁹



(Eq. 181). α -Dioximes are very easily oxidized to furoxans¹⁹⁰ (Eq. 182). Oxygen adsorbed on active charcoal containing traces of iron has been observed to bring about geometrical inversion of the less stable isomers of oximes to the more stable one, purportedly through addition of oxygen to one side of the nitrogen while the original oxygen departs from the other.¹⁹¹

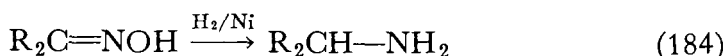


REDUCTION Reduction of oximes can be accomplished by a variety of reagents and usually leads through imines to primary amines; secondary amines may arise by aminolytic equilibration between imine and primary amine during the reaction if reduction is not fast. Stannous chloride and dry, ethereal hydrogen chloride reduce oximes cleanly to imine hydrochlorides without further reductions¹⁹² (Eq. 183). Catalytic hydrogenation (Raney Ni or Pd) usually leads to high yields of primary amine⁵⁰



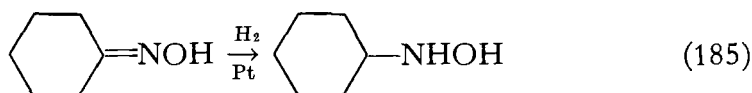
(Eq. 184); if secondary amine formation interferes appreciably, it can be reduced by hydrogenation in the presence of ammonia. Dissolving metals, such as zinc and formic or acetic acid, nickel-aluminum alloy

and alkali, or aluminum amalgam and wet ether, also reduce oximes to primary amines, often in high yield. The formation of amines evidently does not go through initial hydrogenation of the double bond to form an

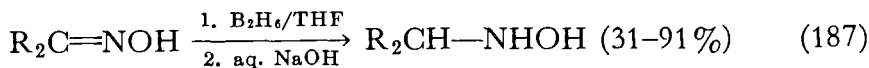
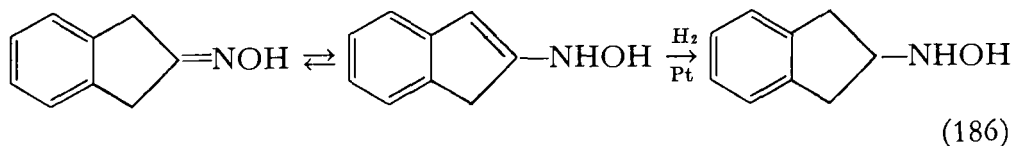


alkyl hydroxylamine, for hydroxylamines are largely inert to hydrogenation; furthermore, imines can in some cases be isolated by interrupting the hydrogenation. An extensive study of the reduction of 2-indanone oximes^{50b} leads to the conclusion that N—O hydrogenolysis is always the first step in the absence of acid.

Reduction of oximes to hydroxylamines by catalytic hydrogenation has only been accomplished in exceptional cases^{50c} (Eq. 185); cyclohexanone oxime is one of the few successful examples.¹⁹³ The hydrogenation of 2-indanone oxime has been manipulated so as to yield up to 54% of hydroxylamine^{50b}; the most favorable conditions are an acidic medium

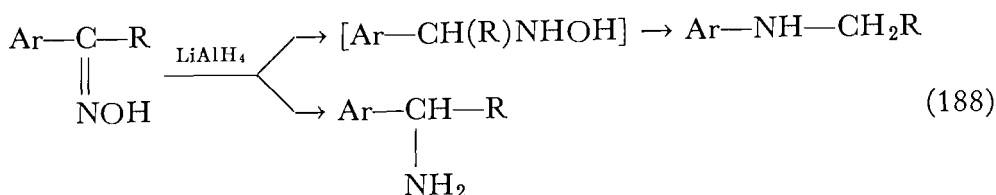


and a platinum catalyst. It is believed that hydroxylamine formation depends on the preferential hydrogenation of the C=C double bond in the small amount of enamine tautomer presumed to be in equilibrium with the oxime; acid promotes equilibration, and a platinum catalyst favors reduction of the ethylenic bond. One would expect, consequently, that structural features that would favor the formation of more of the enamine tautomer than usual would thereby favor hydroxylamine formation (Eq. 186). The most general method for reducing oximes to hydroxylamines is to treat them with diborane,⁵¹ however (Eq. 187).



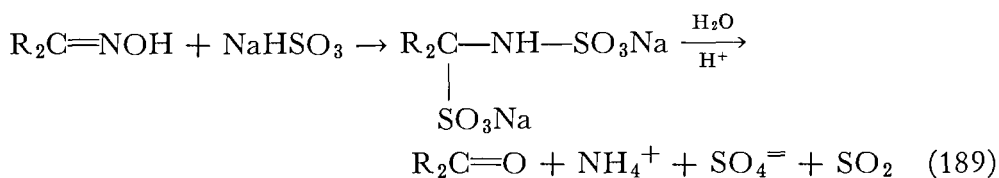
Lithium aluminum hydride attacks oximes only with difficulty; primary amines are usually the eventual product, but migration of a group from C to N is often a side reaction.^{194, 195} In some cases, indeed, it may become the major reaction; the actual product is then the secondary amine derived by reductive rearrangement of the presumed intermediate

hydroxylamine³⁶ (Eq. 188). Aryl alkyl ketoximes are particularly susceptible to such rearrangement, and lithium aluminum hydride plus

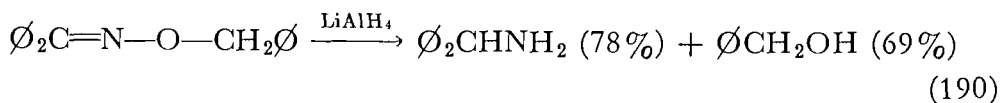


aluminum chloride favors it. There is no difference in result between *syn*- and *anti*-isomers of the oxime. As was pointed out in connection with the action of Grignard reagents, this rearrangement appears to be but one manifestation of such action caused by organometallic reagents.

Sodium bisulfite and sulfur dioxide add to oximes to form isolable addition compounds, whose hydrolysis products show that their formation has involved reduction¹⁹⁶ (Eq. 189); presumably, the addition products are sulfamic acid derivatives, formed in the same way as in the action of bisulfite on hydroxylamine.

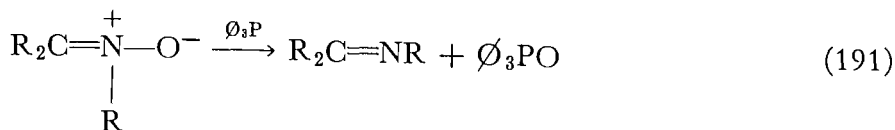


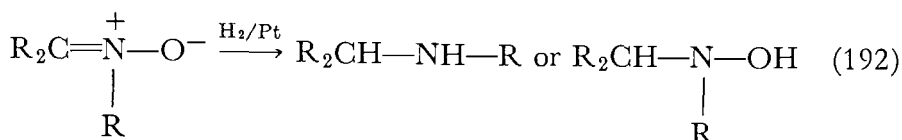
O-Alkyl oximes are generally reduced to primary amines by the same reagents that reduce oximes, including lithium aluminum hydride^{59, 197}; the O-substituent appears as alcohol (Eq. 190). O-Acyl oximes behave similarly.⁵⁹ Small amounts of O,N-dialkyl hydroxylamines have some-



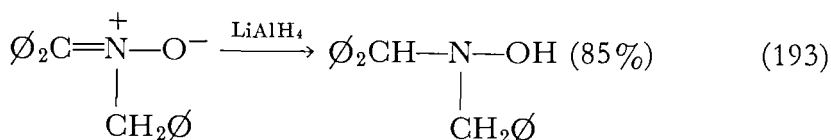
times been obtained by hydrogenation of O-alkyl oximes over platinum.^{197a}

The reduction of nitrones may give imines, secondary amines, or N,N-disubstituted hydroxylamines. Simple deoxygenation can be brought about with such reagents as triphenylphosphine¹⁹⁸ (Eq. 191). Catalytic hydrogenation or tin and hydrochloric acid give secondary amines^{120, 199} or hydroxylamines⁵⁸ (Eq. 192); the latter are formed in good yield by reduction with lithium aluminum hydride or potassium borohydride^{33, 48b, 59}





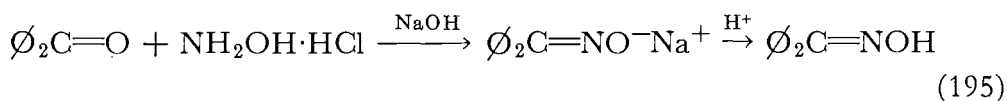
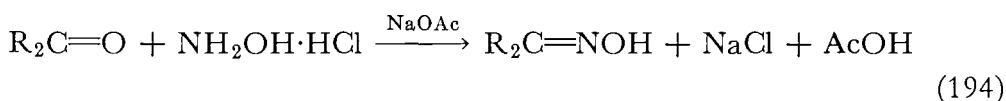
(Eq. 193). A pinacol-type reduction product has been obtained in one



case in low yield by reduction with sodium-potassium alloy in diglyme.²⁰⁰

PREPARATIVE METHODS

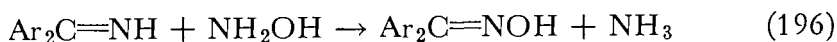
OXIMES By far the vast majority of oximes have been prepared by reaction of aldehydes and ketones with hydroxylamine. It is ordinarily carried out in aqueous-alcoholic solution at temperatures between ambient and refluxing, in the weakly acidic solution provided by adding sodium acetate to hydroxylamine hydrochloride (Eq. 194). Such conditions approach the optimum pH (for acetone, 4.7).¹⁴¹ The rate of oxime formation becomes rapid in strongly alkaline solution also, and oximes can be conveniently prepared in sodium hydroxide solution^{134a} (Eq. 195). Several examples of oximation procedures have been described in detail.²⁰¹



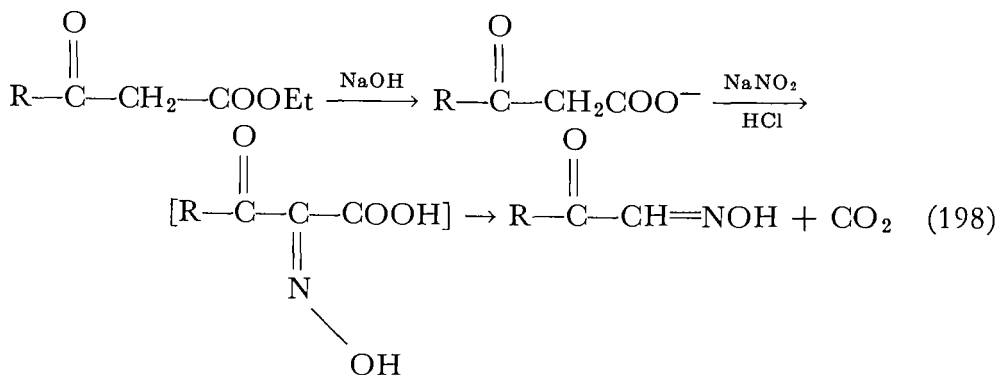
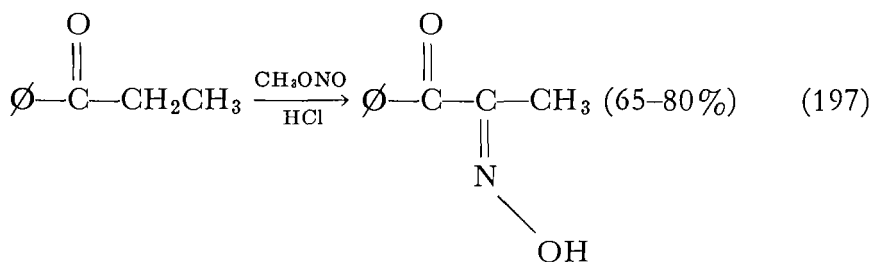
With ordinary, unhindered aldehydes and ketones, addition of NH_2OH to the carbonyl group is rapid, and the rate-determining step is loss of water from the tetrahedral intermediate, $\text{R}_2\text{C}(\text{OH})\text{NHOH}$.^{141c} With severely hindered carbonyl groups, the addition step may become rate determining, making the whole process very slow indeed. Several techniques have been evolved for dealing with such cases. Refluxing in pyridine with hydroxylamine hydrochloride is quite effective, but fails with the most severely hindered cases, such as benzoylmesitylene. Forcing such reactions by high temperatures or prolonged refluxing often leads to Beckmann rearrangement.²⁰² More satisfactory results have been obtained by treating such ketones with hydroxylamine and potas-

sium *tert*-amyloxide at an ambient temperature for long periods (10 days to 15 months).²⁰² Heating under very high pressure has also been used.²⁰³

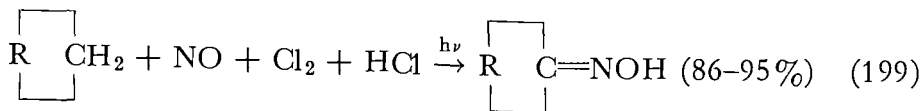
Ketimines react with hydroxylamine to form oximes apparently somewhat more readily than do ketones²⁰⁴ and are useful for the purpose especially when they can be made by reaction of a Grignard reagent with a nitrile.



C-Nitrosation²⁰⁵ is perhaps the next most widely used preparative method for oximes. It requires an active methylene group and is most useful for preparing α -ketooximes from ketones (Eq. 197). It can be accomplished under both acidic and basic conditions, the latter by use of alkyl nitrites.^{206, 207} β -Keto esters are readily nitrosated by first hydrolyzing them to the salt of the β -keto acid, followed by treatment with sodium nitrite and acid; the α -oximino acid formed decarboxylates spontaneously²⁰⁸ (Eq. 198).



Photolytic C-nitrosation can be carried out in high yield on completely nonactivated, saturated hydrocarbons, such as cyclohexane²⁰⁹ (Eq. 199). Although it is simple and efficient, its application is limited largely to cycloalkanes by its lack of specificity. The process involves the rearrangement of nitroso compounds, which often occurs spontaneously, and can be

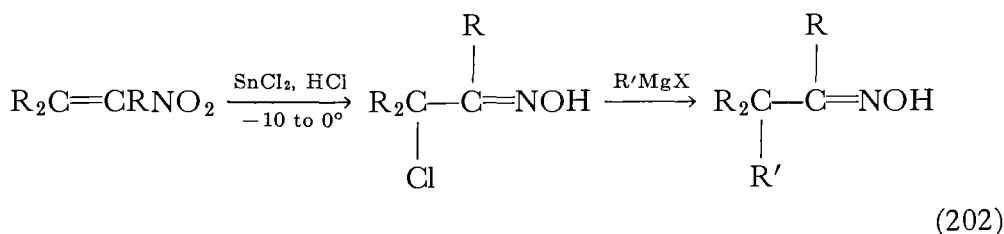
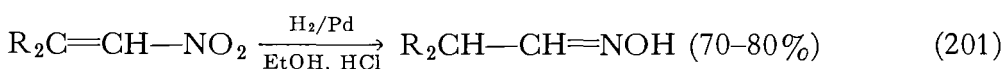


catalyzed by acid or base (see Chapter 13). Nitroso compounds from any source can be used to prepare oximes; although the conversion occurs in very high yields, it is seldom of preparative value as applied to separately isolated nitroso compounds, owing to the difficulty of obtaining them.

The reduction of aliphatic nitro compounds can be conducted so as to yield oximes; to achieve this result, it is necessary to reduce the sodium salts (Eq. 200), even though the actual reducing conditions may be acidic.²¹⁰ Stannous chloride, aluminum amalgam, sodium amalgam, sodium and alcohol, and zinc and alkali are among the reducing agents that have been used. Nitro olefins also yield oximes on reduction (Eq. 201); hydrogenation in

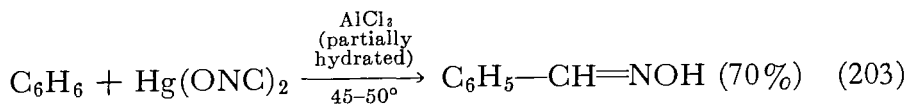


alcoholic hydrochloric acid is the method, and the sodium salt is not required.²¹¹ Reduction with stannous chloride gives good yields of α -chloro oximes, which are sources of larger oximes through replacement of the chlorine by means of Grignard reagents²¹² (Eq. 202).



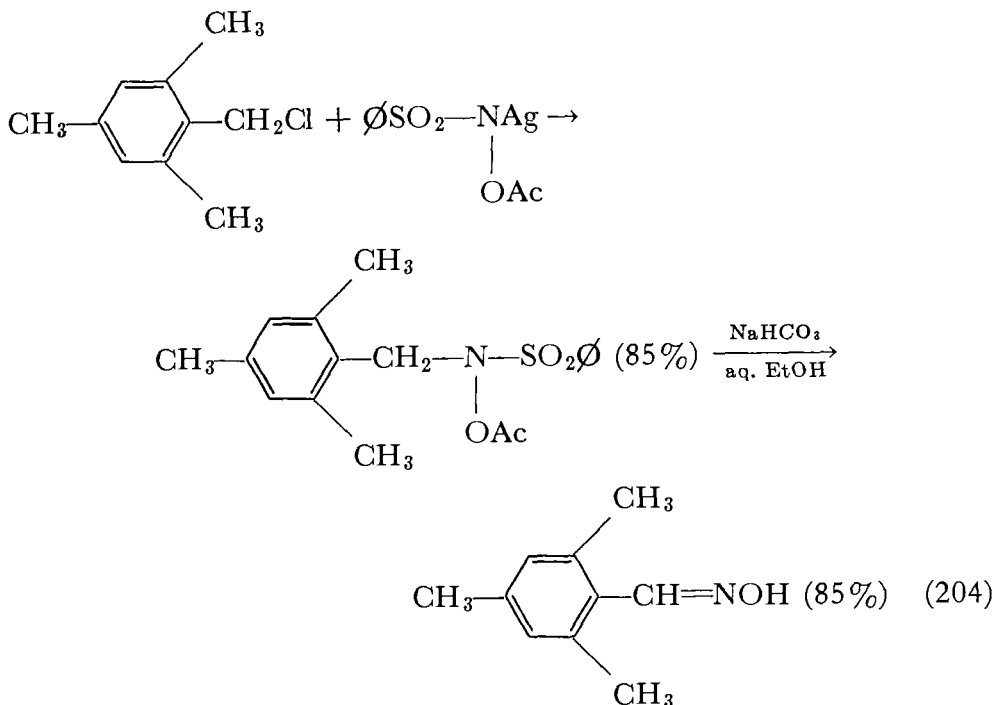
Geminal chloronitroso compounds can be reduced to oximes, presumably through the nitroso alkane, by catalytic hydrogenation (70–86% yields, PtO_2 catalyst) or by sodium borohydride (50–78% yields).²¹³ Although the yields are good, the preparative value of the reaction is severely restricted by the limited availability of the starting materials.

A number of benzaldoximes have been prepared by a Friedel-Crafts type of reaction with fulminic acid²¹⁴ (Eq. 203). Yields are good and the method is very direct, but most chemists prefer to avoid unnecessary meddling with the required reagent.

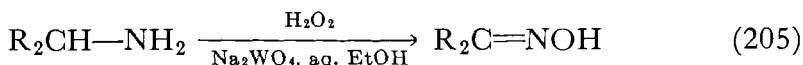


The direct conversion of the more reactive alkyl halides to oximes in good yield by alkylation and hydrolysis of O-acetyl- or O-tetrahydropyranyl-benzenesulfonhydroxamic acid has been reported²¹⁵ (Eq. 204);

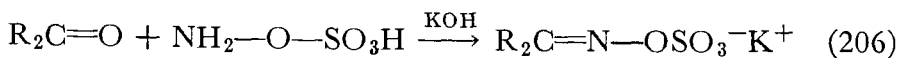
since the reagents require some effort to obtain, the method is of value only in special cases.



Oxidation of primary amines by hydrogen peroxide in the presence of sodium tungstate gives highly variable yields of oximes, but in favorable instances is of definite preparative value ²¹⁶ (Eq. 205).

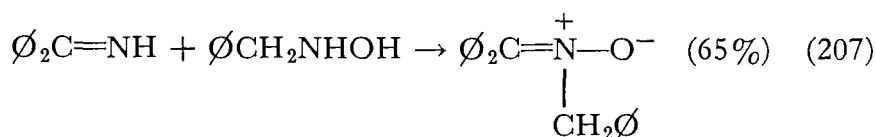


O-SUBSTITUTED OXIMES O-Alkyl oximes can quite generally be prepared by alkylation of oximes, as has been discussed under the heading of reactions. Alternatively, they can be prepared by reaction of O-alkyl hydroxylamines with aldehydes or ketones or by oxidation of O,N-dialkyl hydroxylamines (see section on Hydroxylamines, Reactions). O-Acyl oximes are nearly always prepared by acylation of oximes in the presence of base with acid chlorides. The alternative route, reaction of an O-acyl hydroxylamine with an aldehyde or ketone, is only rarely applicable, because of the difficulty of obtaining the reagents. One of the few examples is the preparation of salts of oxime-O-sulfonic acids ²¹⁷ (Eq. 206).



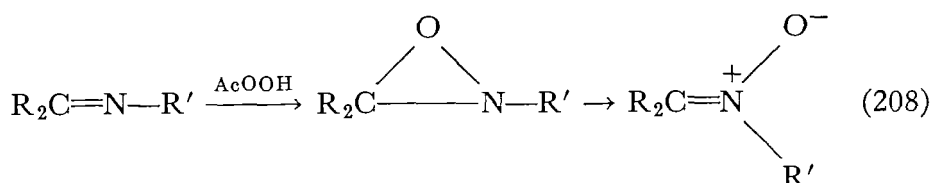
NITRONES The most widely used preparative method for nitrones ¹³³ is alkylation of oximes, followed by separation by recrystallization from the simultaneously produced O-alkyl oximes. The proportion of nitrone

to O-alkyl oxime is more often than not unfavorable, however, and the separation can be difficult. The direct reaction of N-substituted hydroxylamines or their salts with aldehydes or ketones ^{17d} has the advantage of producing a uniform product, and is favored when the requisite hydroxylamine is available (Eqs. 19, 21) (see section on Hydroxylamines, Reactions). N-Aryl oximes are available by this method. With ketones that are sluggish, ketals ^{17d} or ketimines ¹³⁵ give better results (Eq. 207).

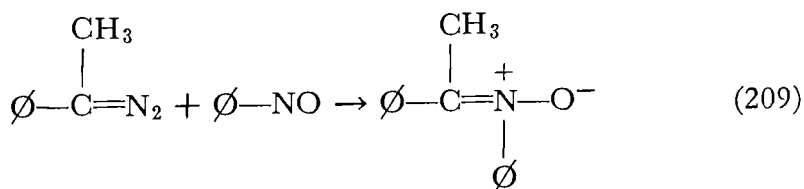


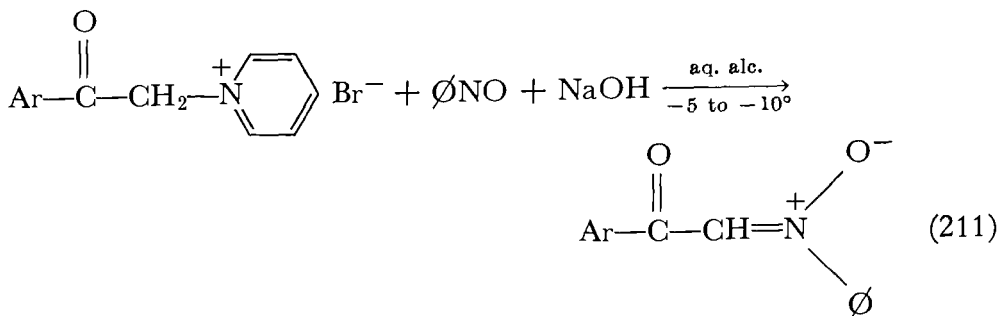
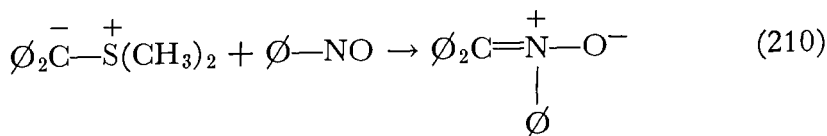
Oxidation of N,N-disubstituted hydroxylamines (Eq. 43) is a useful preparative method for nitrones ^{32c, 48b} when only one compound can result, as when both substituents are the same, or when one is not oxidizable. Air with a cuprammonium catalyst is a favored reagent, but ferricyanide and mercuric oxide also work well.

N-Substituted imines can be oxidized to oxaziridines, which are easily isomerized to nitrones, by peroxy acids ²¹⁸ (Eq. 208). The isomerization may even be spontaneous under the reaction conditions.



Nitroso compounds can be converted to nitrones by reaction with diazo compounds ^{219a} (Eq. 209), sulfonium ylides ²¹⁸ (Eq. 210), or phenacyl pyridinium salts ^{219b} (Eq. 211); these methods are particularly suitable for the preparation of N-aryl oximes. The reactions are usually spontaneous and exothermic; in the diazo reaction, the color change from the dark reds of the diazo alkane and the blue-green of the nitroso compound to the pale yellow of the products is so spectacular that the reaction can be carried out as a self-indicating titration.





HYDROXYLAMINE DERIVATIVES OF THE CARBOXYL GROUP

NOMENCLATURE

The variety of acyl derivatives of hydroxylamine is surprisingly great, and the nomenclature correspondingly complex. All possible combinations of amides, imidic acid derivatives, amidines, imides, and imidic carboxylic anhydrides with N-hydroxy, N-alkoxy, or N-acyloxy groups have to be considered.

N-Monoacyl hydroxylamines, R—CONHOH , are known as hydroxamic acids and are named by replacing the final -ic of the parent carboxylic acid name by the suffix -hydroxamic; thus "benzohydroxamic acid," $\phi\text{—CONHOH}$. The tautomeric forms, $\text{R—C}(\text{OH})=\text{NOH}$, known only in the form of derivatives or as participants in labile equilibria in solution, are called hydroximic acids, and the radicals derived from

them, $\text{R—C}=\text{NOH}$, hydroximoyl groups. On the basis of these, systematic names for the more complicated derivatives can be built up. The possible structures and a variety of acceptable names are set out schematically here using benzoic acid derivatives for illustration. Although some of the names are rather awkward, so is the job they have to do, and they all have the prime requisite of being unambiguous and also fairly systematic. Some of these structural types have received so little attention, at least in the 20th century, that it has not been necessary for the I.U.P.A.C. Nomenclature Commission or *Chemical Abstracts* to make use of names for them, although their principles can be utilized to produce suitable names. The suggested names are given in an order of decreasing preference as viewed subjectively by one organic chemist; where a dif-

ferent preference has been shown elsewhere, this is indicated. In addition to the names given, most of the structures can be named as substitution products of the corresponding simple ammonia derivatives, by use of the prefixes N-hydroxy, N-alkoxy, or N-acyloxy, as in "N-hydroxy benza-mide" for benzohydroxamic acid. The important thing is not so much to use a particular name, but to avoid using a name that is incorrect because of being ambiguous or misleading

For the purpose of clarity, the Roman numerals keyed to the type structures in Table 8-3 will be used in the remainder of this chapter along with specific names, since the names themselves are often as much of a hindrance as a help, and most chemists will more readily comprehend structures in the complicated cases.

Table 8-3
Hydroxylamine derivatives of the carboxyl group

$\begin{array}{c} \text{O} \\ \parallel \\ \text{Ø}-\text{C}-\text{NHOH} \end{array}$ benzohydroxamic acid I	$\begin{array}{c} \text{OH} \\ \\ \text{Ø}-\text{C}=\text{NOH} \end{array}$ benzohydroximic acid II	$\begin{array}{c} \text{O} \\ \parallel \\ \text{Ø}-\text{C}-\text{N}-\text{OH} \\ \\ \text{R} \end{array}$ N-alkylbenzohydroxamic acid (<i>Chem. Abstr.</i>, inverted) III
$\begin{array}{c} \text{O} \\ \parallel \\ \text{Ø}-\text{C}-\text{NHO}-\text{R} \end{array}$ alkyl benzohydroxamate (<i>Chem. Abstr.</i>, inverted); O-alkylbenzohydroxamic acid IV	$\begin{array}{c} \text{OH} \\ \\ \text{Ø}-\text{C}=\text{NO}-\text{R} \end{array}$ benzalkoximic acid V	$\begin{array}{c} \text{OR} \\ \\ \text{Ø}-\text{C}=\text{NOH} \end{array}$ alkyl benzohydroximate; alkyl benzoate oxime (<i>Chem. Abstr.</i>, inverted) VI
$\begin{array}{c} \text{O} \\ \parallel \\ \text{Ø}-\text{C}-\text{N}-\text{OR} \\ \\ \text{R} \end{array}$ alkyl N-alkyl-benzohydroxamate (<i>Chem. Abstr.</i>, inverted); O,N-dialkylbenzohydroxamic acid VII	$\begin{array}{c} \text{OR} \\ \\ \text{Ø}-\text{C}=\text{NO}-\text{R} \end{array}$ alkyl benzalkoximate; alkyl benzoate O-alkyl-oxime; alkyl O-alkylbenzhydroximate VIII	$\begin{array}{c} \text{Cl} \\ \\ \text{Ø}-\text{C}=\text{NOH} \end{array}$ benzohydroxim(o)yl chloride (<i>Chem. Abstr.</i>, 3d Decennial Index) (I.U.P.A.C.); benzoyl chloride oxime (<i>Chem. Abstr.</i>, 4th Decennial and after) IX

Table 8-3 (Continued)

$\begin{array}{c} \text{Cl} \\ \\ \phi - \text{C} = \text{NO} - \text{R} \end{array}$ benzalkoxim(o)yl chloride; O-alkyl-benzhydroxim(o)yl chloride; benzoyl chloride O-alkyloxime X	$\begin{array}{c} \text{Cl} \quad \quad \text{O} \\ \quad \quad \parallel \\ \phi - \text{C} = \text{NO} - \text{C} - \phi \end{array}$ benzobenzoyloxyim(o)yl chloride; O-benzoylbenzo- hydroximoyl chloride; benzoyl chloride O-benzoyl- oxime XI	
$\begin{array}{c} \text{O} \quad \quad \text{O} \\ \parallel \quad \parallel \\ \phi - \text{C} - \text{NHO} - \text{C} - \phi \end{array}$ O,N-dibenzoylhydroxyl- amine; dibenzhydroxamic acid XII	$\begin{array}{c} \text{O} \\ \parallel \\ \text{O} - \text{C} - \phi \\ \\ \phi - \text{C} = \text{NOH} \end{array}$ benzoic benzohydroximic anhydride; benzoic anhy- dride (mon)oxime XIII	$\begin{array}{c} \text{O} \\ \parallel \\ \text{O} - \text{C} - \phi \\ \\ \phi - \text{C} = \text{NO} - \text{R} \end{array}$ benzoic benzalkoximic anhydride; benzoic anhy- dride O-alkyloxime XIV
$\begin{array}{c} \text{OH} \quad \quad \text{O} \\ \quad \quad \parallel \\ \phi - \text{C} = \text{NO} - \text{C} - \phi \end{array}$ benzobenzoyloximic acid XV	$\begin{array}{c} \text{OR} \quad \quad \text{O} \\ \quad \quad \parallel \\ \phi - \text{C} = \text{NO} - \text{C} - \phi \end{array}$ alkyl benzobenzoyloxi- mate; alkyl benzoate O-benzoyl-oxime XVI	$\begin{array}{c} \text{O} \quad \quad \text{O} \\ \parallel \quad \parallel \\ \phi - \text{C} - \text{N} - \text{O} - \text{C} - \phi \\ \\ \text{R} \end{array}$ N-alkyl-O,N-dibenzoyl hydroxylamine XVII
$\begin{array}{c} \text{O} \\ \parallel \\ \phi - \text{C} \\ \quad \quad \diagdown \\ \quad \quad \text{N} - \text{OH} \\ \quad \quad \diagup \\ \phi - \text{C} \\ \parallel \\ \text{O} \end{array}$ N,N-dibenzoylhydroxyl- amine; N-hydroxydibenz- amide (<i>Chem. Abstr.</i>, in- verted) XVIII	$\begin{array}{c} \text{O} \quad \quad \text{O} \\ \parallel \quad \parallel \\ \phi - \text{C} \quad \quad \text{O} - \text{C} - \phi \\ \quad \quad \diagdown \quad \diagup \\ \quad \quad \text{N} - \text{O} \\ \quad \quad \diagup \quad \diagdown \\ \phi - \text{O} \quad \quad \text{C} \\ \parallel \\ \text{O} \end{array}$ tribenzoylhydroxylamine XIX	$\begin{array}{c} \text{O} = \text{C} - \phi \\ \\ \text{O} \\ \\ \phi - \text{C} = \text{NO} - \text{C} - \phi \\ \parallel \\ \text{O} \end{array}$ benzoic benzobenzoylox- imic anhydride; benzoic anhydride O-benzoyl- oxime; O,O'-dibenzoyl- benzohydroximic acid XX

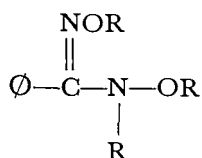
Table 8-3 (Continued)

$\begin{array}{c} \text{O} \\ \\ \phi - \text{C} - \text{ONH}_2 \end{array}$ O-benzoylhydroxylamine; benzoyloxyamine XXI	$\begin{array}{c} \text{O} \\ \\ \phi - \text{C} - \text{ONH}-\text{R} \end{array}$ O-benzoyl-N-alkyl hydroxylamine; benzoyloxy-N-alkylamine XXII	$\begin{array}{c} \text{O} \\ \\ \phi - \text{C} - \text{ONR}_2 \end{array}$ O-benzoyl-N,N-dialkylhydroxylamine; benzoyloxy-N,N-dialkylamine XXIII
$\begin{array}{c} \text{NH} \\ \\ \phi - \text{C} - \text{ONH}_2 \end{array}$ O-benzimidoylhydroxylamine; benzimidoyloxyamine XXIV	$\begin{array}{c} \text{NH} \\ \\ \phi - \text{C} - \text{ONH}-\text{R} \end{array}$ O-benzimidoyl-N-alkylhydroxylamine; benzimidoyloxy-N-alkylamine XXV	$\begin{array}{c} \text{NH} \\ \\ \phi - \text{C} - \text{ONR}_2 \end{array}$ O-benzimidoyl-N,N-dialkylhydroxylamine; benzimidoyloxy-N,N-dialkylamine XXVI
$\begin{array}{c} \text{NR} \\ \\ \phi - \text{C} - \text{ONH}_2 \end{array}$ O-(N-alkylbenzimidoyl)hydroxylamine; N-alkylbenzimidoyloxyamine XXVII	$\begin{array}{c} \text{NR} \\ \\ \phi - \text{C} - \text{ONH}-\text{R} \end{array}$ O-(N-alkylbenzimidoyl)-N-alkylhydroxylamine XXVIII	$\begin{array}{c} \text{NR} \\ \\ \phi - \text{C} - \text{ONR}_2 \end{array}$ O-(N-alkylbenzimidoyl)-N,N-dialkylhydroxylamine XXIX
$\begin{array}{c} \text{NOH} \\ \\ \phi - \text{C} - \text{ONH}_2 \end{array}$ O-benzohydroximoylhydroxylamine XXX	$\begin{array}{c} \text{NOH} \\ \\ \phi - \text{C} - \text{ONH}-\text{R} \end{array}$ O-benzohydroximoyl-N-alkylhydroxylamine XXXI	$\begin{array}{c} \text{NOH} \\ \\ \phi - \text{C} - \text{ONR}_2 \end{array}$ O-benzohydroximoyl-N,N-dialkylhydroxylamine XXXII
$\begin{array}{c} \text{NO}-\text{R} \\ \\ \phi - \text{C} - \text{ONH}_2 \end{array}$ O-benzalkoximoylhydroxylamine XXXIII	$\begin{array}{c} \text{NO}-\text{R} \\ \\ \phi - \text{C} - \text{ONH}-\text{R} \end{array}$ O-benzalkoximoyl-N-alkylhydroxylamine XXXIV	$\begin{array}{c} \text{NO}-\text{R} \\ \\ \phi - \text{C} - \text{ONR}_2 \end{array}$ O-benzalkoximoyl-N,N-dialkylhydroxylamine XXXV
$\begin{array}{c} \text{NOH} \\ \\ \phi - \text{C} - \text{NH}_2 \end{array}$ benzaminoxime; benzhydroximamide XXXVI	$\begin{array}{c} \text{NH} \\ \\ \phi - \text{C} - \text{NHOH} \end{array}$ benzimidohydroxamic acid; N-benzimidoylhydroxylamine XXXVII	$\begin{array}{c} \text{NH}_2 \\ \\ \phi - \text{C} = \text{NO}-\text{R} \end{array}$ O-alkylbenzaminoxime; O-alkylbenzhydroximamide; benzalkoximamide XXXVIII

Table 8-3 (Continued)

$\begin{array}{c} \text{NHR} \\ \\ \phi - \text{C} = \text{NOH} \end{array}$ N-Alkylbenzamidoxime; N-alkylbenzhydroxim- amide XXXIX	$\begin{array}{c} \text{NR} \\ \\ \phi - \text{C} - \text{NHOH} \end{array}$ N-(N-alkylbenzimidoyl)- hydroxylamine XL	$\begin{array}{c} \text{NR} \\ \\ \phi - \text{C} - \text{N} - \text{OH} \\ \\ \text{R} \end{array}$ N-(N-alkylbenzimidoyl)- N-alkylhydroxylamine XLI
$\begin{array}{c} \text{NH} \\ \\ \phi - \text{C} - \text{NHO} - \text{R} \end{array}$ O-alkyl-N-benzimidoylhy- droxylamine; alkyl benzi- midohydroxamate XLII	$\begin{array}{c} \text{NR} \\ \\ \phi - \text{C} - \text{NHO} - \text{R} \end{array}$ O-alkyl-N-(N-alkylbenzi- midoyl)hydroxylamine XLIII	$\begin{array}{c} \text{NH} - \text{R} \\ \\ \phi - \text{C} = \text{NO} - \text{R} \end{array}$ O,N'-dialkylbenzamid- oxime; benzalkoximido- (N-)alkylamide XLIV
$\begin{array}{c} \text{NR}_2 \\ \\ \phi - \text{C} = \text{NO} - \text{R} \end{array}$ benzalkoximidodialkyl- amide; O-alkyl-N',N'-di- alkyl benzamidoxime; benzodialkylamide O-alkyl- oxime XLV	$\begin{array}{c} \text{NH}_2 \quad \text{O} \\ \quad \\ \phi - \text{C} = \text{NO} - \text{C} - \phi \end{array}$ benzobenzoyloximamide; O-benzoylbenzamidoxime XLVI	$\begin{array}{c} \text{O} \\ \\ \text{NH} - \text{C} - \phi \\ \\ \phi - \text{C} = \text{NOH} \end{array}$ dibenzamide monoxime; N-benzoylbenzohydro- ximamide XLVII
$\begin{array}{c} \text{N} - \text{OH} \\ \\ \phi - \text{C} - \text{NHOH} \end{array}$ benzohydroxyamidoxime; benzhydroximohydrox- amic acid; N-benzhydroxi- moylhydroxylamine XLVIII	$\begin{array}{c} \text{NOR} \\ \\ \phi - \text{C} - \text{NHOH} \end{array}$ benzalkoximohy- droxamic acid; N-benz- alkoximoylhydroxylamine XLIX	$\begin{array}{c} \text{NOH} \\ \\ \phi - \text{C} - \text{NHO} - \text{R} \end{array}$ alkyl benzhydroxim- ohydroxamate; N-benzal- koximoylalkoxyamine L
$\begin{array}{c} \text{NOH} \\ \\ \phi - \text{C} - \text{N} - \text{OH} \\ \\ \text{R} \end{array}$ benzohydroximo-N- alkylhydroxamic acid; N- benzohydroximoyl-N- alkylhydroxylamine LI	$\begin{array}{c} \text{NO} - \text{R} \\ \\ \phi - \text{C} - \text{N} - \text{OH} \\ \\ \text{R} \end{array}$ benzalkoximo-N-alkyl- hydroxamic acid; N-benz- alkoximoyl-N-alkyl- hydroxylamine LII	$\begin{array}{c} \text{NOH} \\ \\ \phi - \text{C} - \text{N} - \text{OR} \\ \\ \text{R} \end{array}$ alkyl benzohydroximo- N-alkylhydroxamate; N- benzohydroximoyl-N- alkylalkoxyamine LIII

Table 8-3 (Continued)

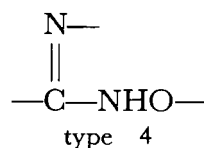
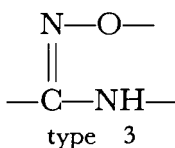
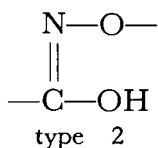
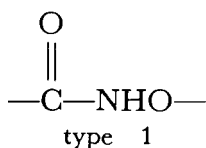


alkyl benzalkoximo-N-
alkylhydroxamate; N-
benzalkoximoyl-N-alkyl-
alkoxyamine

LIV

Plus: N-acyl and/or O-acyl derivatives of XXIV to XXXIV, XXXVII to LIII.

As a final word about the drudgery of nomenclature, it should be mentioned that in the many cases where tautomerism is possible, it usually remains uncertain which tautomer one has in hand, making the proper choice of name ambiguous. It is usual in such cases to make an arbitrary assumption, commonly that in accord with the conclusions from structural evidence about closely related compounds. This nearly always means that type 1 is preferred over type 2 and type 3 over type 4:



PROPERTIES

The elucidation of the separate identities of the large variety of acyl hydroxylamine derivatives was a task of exceptional difficulty and complexity, not just because of the number of structural types, but because so many of the compounds exist in several polymorphic crystalline modifications as well as exhibiting tautomerism and geometric isomerism. The lion's share of the credit must go to W. Lossen and his students, who successfully characterized most of the structures during the last quarter of the 19th century, without benefit of any of the spectroscopic methods of today. Nearly all of Lossen's assignments stand today, most of them confirmed by physical methods, except for a few cases of confusion among polymorphs, tautomers, and geometric isomers. What follows is a brief survey of representative examples.

RCONHOH Unsubstituted hydroxamic acids are solids, such as $\text{CH}_3-\text{CONH}-\text{OH}$, mp 88° , $\text{O}-\text{CONH}-\text{OH}$, mp 132° , and $\text{O}-\text{SO}_2-\text{NH}-\text{OH}$, mp 126° , soluble in water up to a size of about six carbons, and

nearly insoluble in ether when small. They are weak acids, comparable to phenol in strength: $\text{CH}_3\text{—CONH—OH}$, pK_a 9.4; Ø—CONH—OH , pK_a 8.89.^{220–222} They are also very weak bases and form salts with strong acids in nonaqueous media; water hydrolyzes the salts almost completely.¹⁵⁷

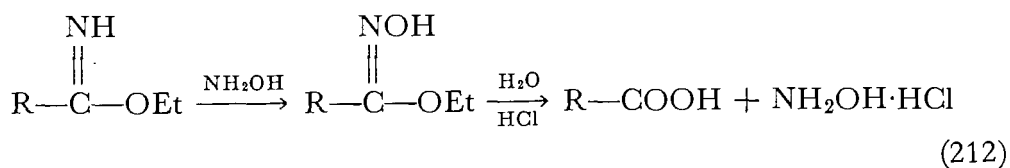
Hydroxamic acids in the solid state in polar solvents have been shown by both ultraviolet^{223, 224} and infrared^{119, 224, 225} spectrography to have the assigned tautomeric structure; amide carbonyl stretching appears at $1650\text{--}1670\text{ cm.}^{-1}$, and N—H stretching is recognizable in addition to O—H . Some equilibration with the enolic, hydroximic acid, form undoubtedly occurs in some solvents. Some hydroxamic acids have been isolated in two modifications, distinguished by different melting points and crystal form, and it has been speculated that these actually might be the tautomers. An investigation²²⁵ of one example, chloroacethydroxamic acid, has shown that the two forms have identical infrared spectra and are thus polymorphic forms rather than tautomers, however. The monoanions RCONHO^- and $\text{RC(=O)NOH}^- \leftrightarrow \text{RC(—O}^-\text{)=NOH}$ appear to be of approximately equal stability in solution.^{222b}

R—CON(R)OH N-Alkylhydroxamic acids, such as $\text{CH}_3\text{—CON(CH}_3\text{)—OH}$, bp $80^\circ/2\text{ mm.}$, are liquids or low-melting solids, and are of moderate acidity ($\text{ØCON(CH}_3\text{)OH}$, pK_a 8.59).^{222b} Some examples have been obtained in two forms. Those of N-phenylbenzohydroxamic acid have been investigated by infrared spectrography²²⁵; the spectra are different in the solid state (C=O at 1637 and 1646 cm.^{-1}), but are identical in solution (C=O at 1630 cm.^{-1}). The differences are believed to be due to restricted rotation about the C—N bond, allowing the fixing of *cis* and *trans* conformations in the crystalline state. The structure of compounds of this type has been adequately established by their preparation by acylation of N-substituted hydroxylamines, and hydrolysis back to them.

R—CONH—OR Alkyl hydroxamates (structure type IV) are known in considerably greater variety than their N-substituted isomers. They are low-melting solids, such as HCONH—OCH_3 , mp 39° , bp $116\text{--}117^\circ/33\text{ mm.}$, and Ø—CONH—OCH_3 , mp 64.5° . They are acidic, and appear to be of similar strength to the parent hydroxamic acids; pK_a for ØCONHOCH_3 is 8.88 and for $\text{HOOC(CH}_2\text{)}_2\text{CONH—OCH}_2\text{Ø}$ (second H^+), 10.2 (cf. pK_a for $\text{HOOC(CH}_2\text{)}_2\text{CONH—OH}$, 9.6).^{222b, 227} A group of O-aryl derivatives of a carbohydroxamic acid, Ar—O—NH—COOEt , have been found to have pK_a 's from 8.6 to 10.4, depending on the substituents on the aryl group.^{68b} The infrared spectra of alkyl hydroxamates^{119, 225, 226} show amide carbonyl stretching at $1630\text{--}1655\text{ cm.}^{-1}$ in the solid state, and $1660\text{--}1690\text{ cm.}^{-1}$ in chloroform solution, but in the case of ethyl benzohydroxamate in carbon tetrachloride solu-

tion, both a carbonyl band (1705 cm^{-1}) and a $\text{C}=\text{N}$ band (1633 cm^{-1}) appear, as well as $\text{N}-\text{H}$ and chelated $\text{O}-\text{H}$. These facts are consistent with the interpretation that the substance is ordinarily in the hydroxamate ester form (IV), but in nonpolar solvents may equilibrate with appreciable concentrations of the enolic tautomer (structure type V). The gross structure of such compounds has been adequately established by preparation from and hydrolysis to alkoxyamines^{226b} in a large variety of instances.

$\text{R}-\text{C}(\text{OR})=\text{NOH}$ Alkyl hydroximates (structure type VI) are usually solids. They are weaker acids than hydroxamic acids by ca. 3 units; $\text{C}(\text{OEt})=\text{NOH}$, for example, has pK_a 11.6. Many of them can be obtained in two forms, as, for example, methyl benzohydroximate, mp 65° and 101° . In several instances these forms have been demonstrated to be geometrical isomers, whose configuration has been established by differences in dipole moment^{228a} or in degree of association in nonpolar solvents^{228b}; the *syn*-alkoxyl isomers are distinctly less associated than the *anti*-, owing to the proximity of the oxygen to the hydroxyl group in the same molecule. The conclusions are reinforced by the fact that the *syn*-isomers undergo the Beckmann rearrangement to give *N*-substituted urethans, whereas the *anti*-alkoxyl isomers do not rearrange.²²⁸ The gross structure of alkyl hydroximates is confirmed by the facts that their dry hydrochlorides on warming cleave to a hydroxamic acid and alkyl chloride and acid-catalyzed hydrolysis gives hydroxylamine.²²⁹ In addition, they can be prepared from the reaction of imidate esters with hydroxylamine²³⁰ (Eq. 212). The infrared spectrum of methyl benzo-hydroximate shows $\text{C}=\text{N}$ stretching at 1630 cm^{-1} , vinyl $\text{C}-\text{O}$ at 1320 – 1340 , $\text{O}-\text{H}$ at 3623 cm^{-1} (dilute soln.), and general features similar to ordinary imidate esters.²²⁵



$\text{RCCl}=\text{NOH}$ Hydroximoyl chlorides are liquids or low-melting solids, such as acethydroximoyl chloride, mp -3° , and benzohydroximoyl chloride, mp 52° . They are of pronounced acidity, as shown by oxalhydroximoyl chloride, $\text{HON}=\text{CClCCl}=\text{NOH}$, pK_a 3,¹¹⁴ but easily eliminate hydrogen chloride on standing or treatment with bases. The infrared spectrum of oxalohydroximoyl chloride¹¹⁴ shows $\text{C}=\text{N}$ stretching at 1623 and $\text{N}-\text{O}$ at 1000 cm^{-1} .

$\text{RCONH}-\text{O}-\text{COR}$ *O*, *N*-Diacyl hydroxylamines (type XII) are solids of moderate melting point, such as *O*,*N*-diacetylhydroxylamine, mp 89° ,

and O,N-dibenzoylhydroxylamine, mp 159°. The smaller ones are very soluble in water. They are stronger acids than simple hydroxamic acids, as shown by N-gluconyl-O-benzoylhydroxylamine, pK_a 5.84 compared to gluconohydroxamic acid, pK_a 8.94²³¹; O,N-dibenzoylhydroxylamine, however, is precipitated from its salts by carbonic acid. The infrared spectra show N—H stretching and two carbonyl stretching bands; for the dibenzoyl compound, they are at 1650 cm^{-1} and 1772 cm^{-1} , corresponding, respectively, to amide and ester carbonyl.^{224, 225} Apart from the spectral evidence, O,N-diacyl hydroxylamines are distinguishable from the N,N-diacyl isomers by their preparation by dealkylation of alkyl acyloximates (type XVI) with hydrogen chloride,²³² by the fact that the examples with two different acyl groups can be obtained as structural isomers, depending on the order of entry of the acyl groups,²³² and by profound chemical differences, the occurrence of the Lossen rearrangement in particular.

TRIACYLHYDROXYLAMINES The triacyl derivatives of hydroxylamine (types XIX and XX) are either oils, such as triacetylhydroxylamine, bp 216° with decomposition, or solids of moderate melting point, such as acetic benzobenzoyloxyimide anhydride, mp 84–85°. The tribenzoyl derivatives of hydroxylamine are known in three forms; α , mp 100°; β , mp 141–142°; and γ , mp 112°.²³² The α form shows infrared absorption at 1776 cm^{-1} (ester C=O) and 1715 cm^{-1} (amide C=O), and a dipole moment of 3.78 D., whereas the β -form has infrared bands at 1761,

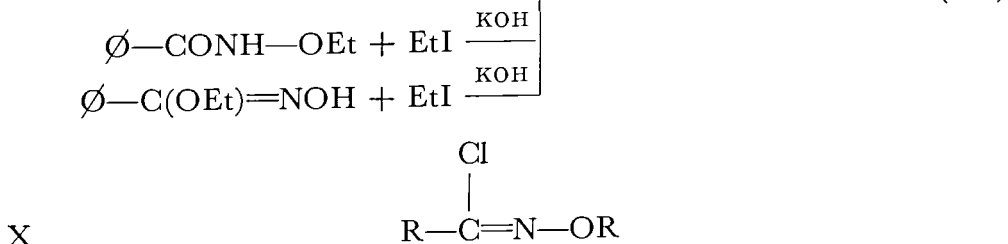
1754, and 1624 cm^{-1} (interpreted as $\text{N}-\text{O}-\overset{\text{O}}{\overset{\text{||}}{\text{C}}}=\text{O}$, $\text{C}-\text{O}-\overset{\text{O}}{\overset{\text{||}}{\text{C}}}=\text{O}$, and C=N), and a dipole moment of 4.84 D.²²⁴ On the basis of these data and ultra violet spectra, the α -form is presumed to be tribenzoyl hydroxylamine, and the β -form benzoic benzobenzoyloximide anhydride (type XX); the γ -form is perhaps a geometrical isomer of the β -form.

AMIDOXIMES The amidoximes are in general solids, very soluble in water and difficultly soluble in ether when small; formamidoxime has mp 114–115°, acetamidoxime, 135°, and benzamidoxime, 80°. They are basic, but less so than amidines; N'-phenylbenzamidoxime is precipitated from its salts by ammonia, for example. Amidoximes also have weak acidic properties, which are lost on O-alkylation; oxamidoxime,^{233a} mp 210°, has $pK_a = 10.6$. Infrared spectra,²³³ which show C=N stretching at 1620–1670 cm^{-1} , are not conclusive as to structure, but in conjunction with nuclear magnetic resonance, which shows OH at 0τ and a single NH signal, twice as strong, at 4.68 τ , lead strongly to the assignment of the amidoxime structure (type XXXVI) rather than its tautomer (type XXXVII). Formamidoxime has been shown by X-ray crystallography²³⁴ to be a planar molecule with strong intermolecular hydrogen bonding; the C—NH₂ distance, 1.33 Å, is close to the C=NOH distance, 1.30 Å, indicating extensive delocalization of pi-electrons within

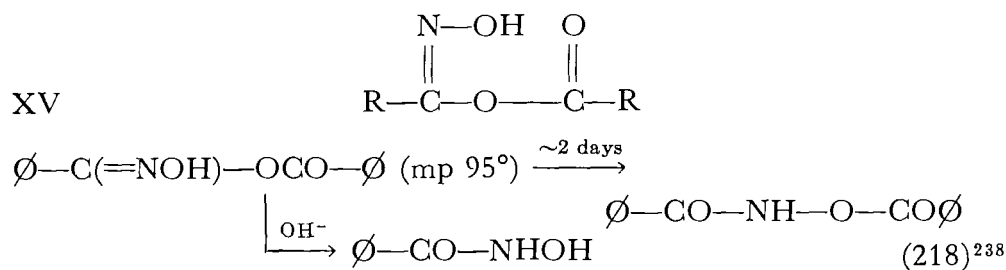
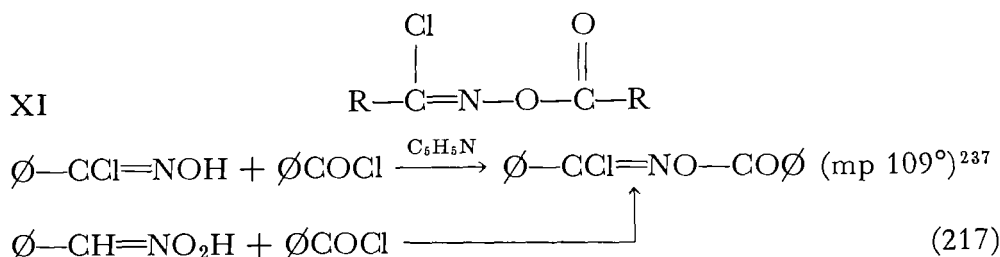
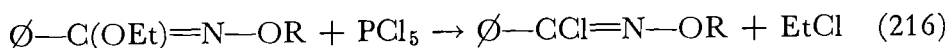
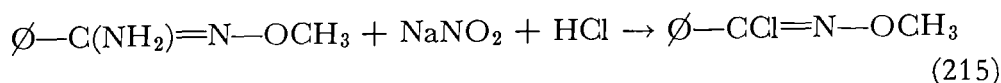
HYDROXYAMIDOXIMES The hydroxyamidoximes (type XLVI) are relatively little known; acethydroxyamidoxime²³⁵ has been reported as an explosive oil that forms a hydrochloride, and benzohydroxyamidoxime is a solid that decomposes at 115° with a great rush of gas.

The remaining varieties of hydroxylamine derivatives of the carboxyl group are too numerous to allow a discussion of each one here. Essential features of a representative collection are summarized in the paragraphs that follow, which include the chemical evidence in the form of synthesis and hydrolysis on which the structure assignments are based.

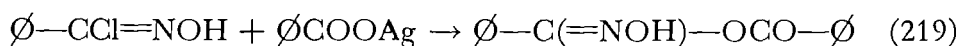

$$\text{C}_6\text{H}_5\text{COCl} + \text{Et}\cdot\text{NH}\cdot\text{OEt} \rightarrow \text{C}_6\text{H}_5\text{CO}\cdot\text{N}(\text{Et})\cdot\text{OEt} \xrightarrow[\Delta]{\text{Conc. HCl}} \text{EtNH}(\text{OEt})\cdot\text{HCl} \quad (213)$$

$$\text{C}_6\text{H}_5\text{CCl}=\text{N}-\text{OEt} + \text{NaOEt} \rightarrow \text{C}_6\text{H}_5-\overset{\text{OEt}}{\underset{\uparrow}{\text{C}}}=\text{NOEt} \xrightarrow[\Delta]{\text{dil. HCl}} \text{EtONH}_2 \cdot \text{HCl} \quad (214)$$


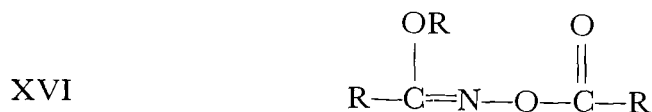
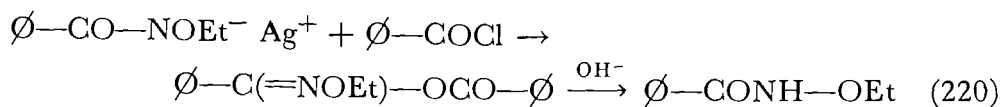
Distillable oils; $\text{HCCl}=\text{N}-\text{OCH}_3$, bp 68° ; $\text{C}_6\text{H}_5\text{CCl}=\text{N}-\text{OCH}_3$, bp 225° .^{232, 236} Geometrical isomers not known.



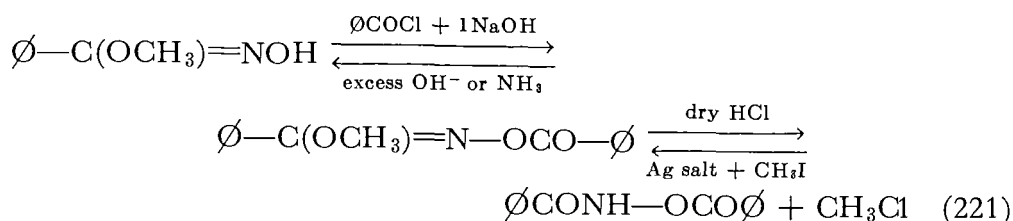
Geometrical isomers not known.



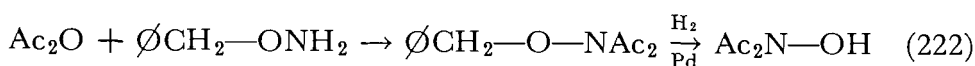
Low-melting solids; $\text{C}_6\text{H}_5-\text{C}(=\text{NOEt})-\text{OCO}-\text{C}_6\text{H}_5$, mp $48-49^\circ$.²³² Geometrical isomers not known.



Low-melting solids; $\text{C}_6\text{H}_5-\text{C}(\text{OCH}_3)=\text{N}-\text{OCO}-\text{C}_6\text{H}_5$, mp 55° .²³² Possible geometrical isomers or polymorphs known.



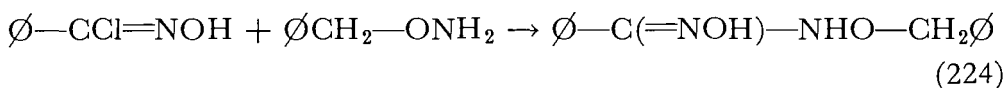
Ac₂N—OH, mp 88.5°; infrared: 1799, 1715, 1608 cm.⁻¹; N-hydroxysuccinimide, mp 94–95°; pK_a 6.0; infrared: 1789, 1709, 1692 cm.⁻¹; N-pentylsuccinimide, 1770, 1706 cm.⁻¹; N-bromosuccinimide, 1821, 1776, 1718 cm.⁻¹.²²⁷



Possible example, NH=C(OH)—ONH₂, tautomer of O-carbamylhydroxylamine, mp 74–75°.²³⁹



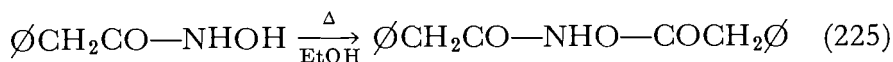
N-Benzoyloxybenzamidoxime, mp 109–110°.²⁴⁰



REACTIONS

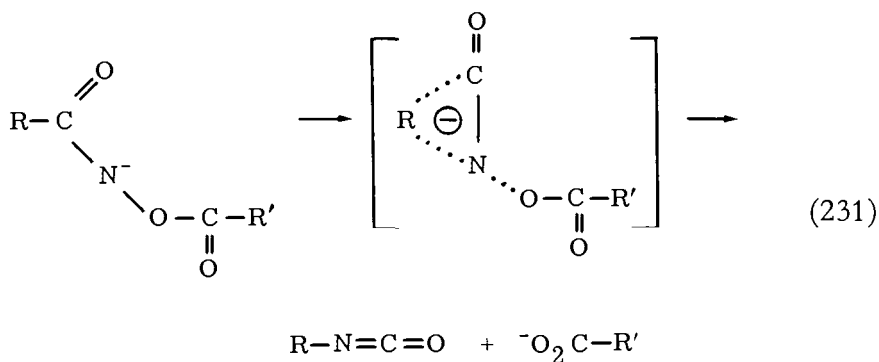
I. Compounds with Only One N

HEAT AND STORAGE Hydroxamic acids and most of their derivatives are stable to ordinary storage, but decompose on strong heating. The simplest change, which can occur even on heating in solvents, is disproportionation, leading to O,N-diacylhydroxylamines²⁴¹ (Eq. 225). This



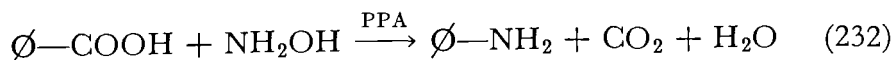
LOSSEN REARRANGEMENT The Lossen rearrangement is probably the dominant single feature of the hydroxamic acids. It is a member of the group of 1,2- C-to-N rearrangements more familiarly represented by the Curtius rearrangement of acyl azides (Chapter 11) and the Hofmann rearrangement of N-haloamide salts (Chapter 4), and is closely related to the Beckmann rearrangement of oximes. Nearly all of the general statements that have been made in those places about the mechanism of those three reactions find their analog with respect to the Lossen rearrangement. The mechanism has been discussed at length elsewhere,^{26b} and only the salient features will be recapitulated here.

The Lossen rearrangement is most efficiently accomplished with O,N-diacylhydroxylamines, and it is thus principally with this class of compound that it has been studied. The salts rearrange enormously faster than the free acids and with first-order kinetics.²⁴⁴ The stronger the acid from which the O-acyl group is derived, the faster the rearrangement^{244a} of the salts. These facts and many more converge upon a mechanism in which the O-acyl group leaves in the form of an anion, with its attached oxygen, in a process concerted with migration of a group from the other carbonyl group to the nitrogen (Eq. 231). When the O-acyl group is derived from a very strong acid, such as a sulfonic or

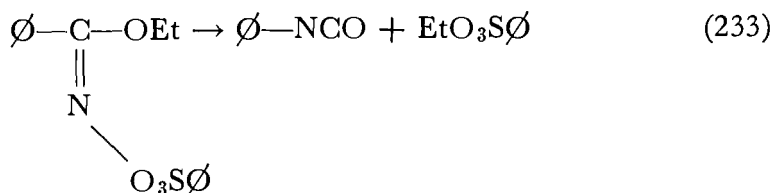


(Mechanism of the Lossen rearrangement)

phosphonic acid, rearrangement is very fast indeed, as would be expected with such good leaving groups, and frequently takes place as fast as such O-acyl derivatives are formed. A convenient way to utilize the Lossen rearrangement for the degradation of a carboxylic acid to an amine is to combine the preparation of the hydroxamic acid, its acylation, and the rearrangement, all in one step, by treating a carboxylic acid with hydroxylamine in warm polyphosphoric acid²⁴⁵ (Eq. 232). Isocyanates may be obtained by treating a hydroxamate salt with excess thionyl chloride in dioxane.^{245b}

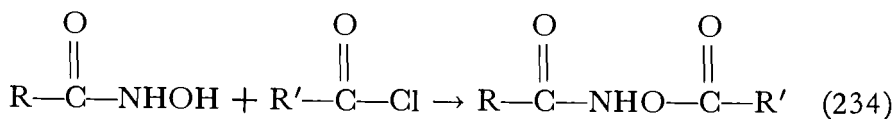


The Lossen type of rearrangement has also been observed with other types of hydroxamic acid analogs, particularly the alkyl hydroximates (type VI) or their acyl derivatives (type XVI). The assignment of configuration to geometrical isomers on this basis ²²⁸ has already been mentioned; the spontaneous rearrangement of ethyl O-benzenesulfonylbenzohydroximate ²⁴⁶ is another example (Eq. 233).

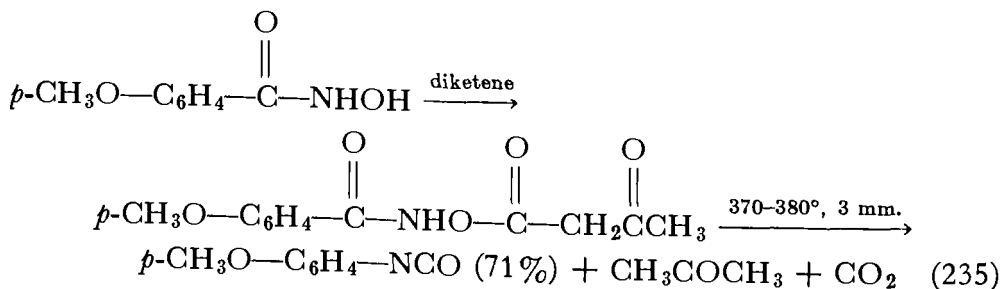


The presence of an N-alkyl group ordinarily prevents occurrence of the Lossen rearrangement,²⁴⁷ although in one case, a cyclic N-substituted hydroxamic acid, N-hydroxyoctahydroisocarbostyryl, the observed ring contraction with loss of carbon dioxide may be a successful example.^{247b} In other cases, loss of carbon monoxide has been observed.^{247b}

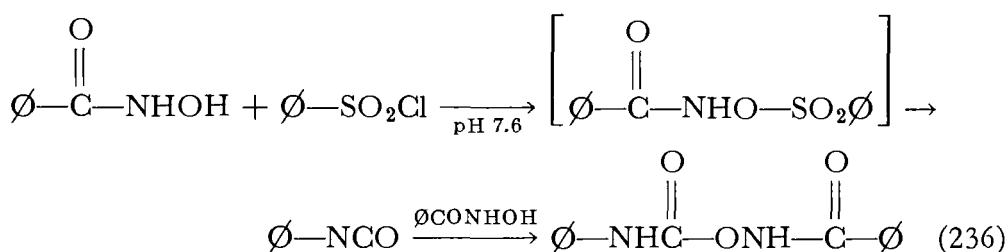
Acylation of N-acyl hydroxylamines almost always takes place on oxygen, if ring formation is not involved, to form O,N-diacyl hydroxylamines, hence the success of the Lossen rearrangement of these compounds as a step in the overall conversion of carboxylic acids or esters through hydroxamic acids to amines, ureas, or isocyanates.²⁴⁸ Not only



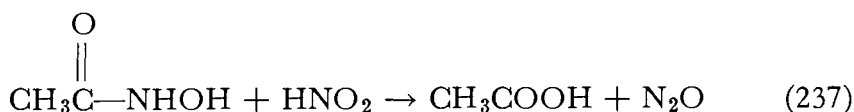
acid chlorides and anhydrides, but also isocyanates, ketene, and diketene can be used as acylating agents.²⁴⁹ In the latter case, a practical isocyanate synthesis results, for the O-acetoacetyl hydroxamic acids that are formed can be broken up by strong heating to form acetone, carbon dioxide, and an isocyanate (Eq. 235).



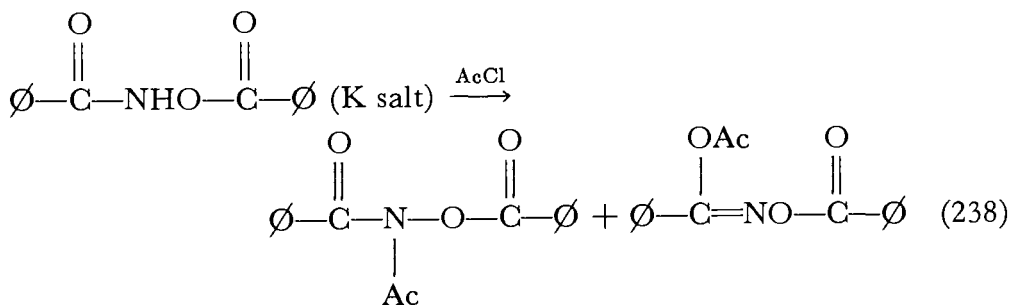
Acylation of simple hydroxamic acids with sulfonyl chlorides has not led to isolable O-acyl compounds; they are almost certainly formed, but their subsequent rearrangement is very rapid.²⁵⁰ The isolated product is likely to be an O-carbamyl N-acyl hydroxylamine, arising through formation of some isocyanate by rearrangement, followed by reaction between isocyanate and untouched hydroxamic acid (Eq. 236). Similar results have been observed with attempted phosphorylation. Nitrosating

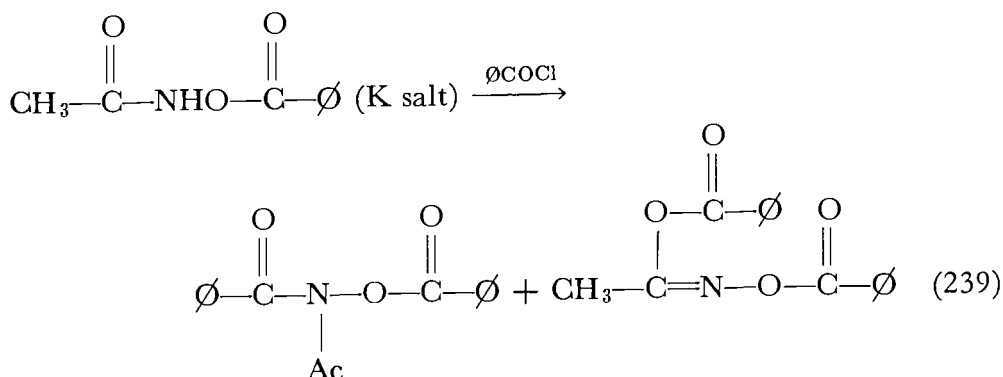


agents presumably form nitroso derivatives with hydroxamic acids, but they are evidently very unstable, for the isolated products are those that might be expected of their decomposition, without rearrangement²⁵¹ (Eq. 237).



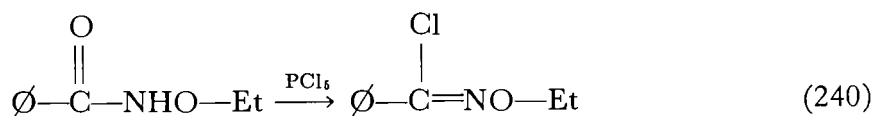
Further acylation of O,N-diacylhydroxylamines (or their alkali metal or silver salts) takes place to a significant extent on both N and O, giving mixtures of N,N,O-triacyl hydroxylamines (type XVIII) and carboxylic acyloximide anhydrides (type XX)²⁵² (Eq. 238). Only rarely have these isomers been separated and identified. The nature of the reaction has been neatly demonstrated by comparing the acetylation of O,N-dibenzoylhydroxylamine with the benzylation of O-benzoyl-N-acetylhydroxylamine²⁵² (Eqs. 238, 239). Each produces a pair of isomers, one of which is identical with that from the other reaction, and must therefore result from N-acylation.



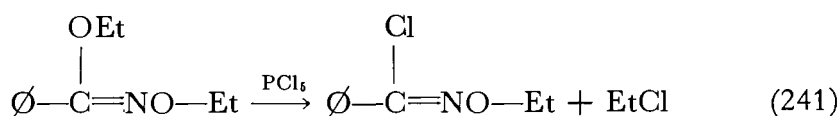


Sulfonhydroxamic acids are apparently acylated first on oxygen, then on nitrogen.²¹⁵

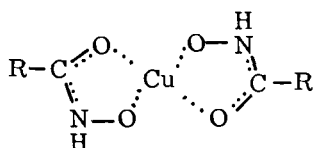
Phosphorus pentachloride acts on alkyl hydroxamates in the same way that it does on N-alkyl amides; the hydroxyl group of the enol tautomer is replaced by chloro, giving an alkoximyl chloride^{229, 253} (Eq. 240). The same compounds are also formed from alkyl alkoximates (type VIII), an



alkyl group being removed as alkyl chloride (Eq. 241).

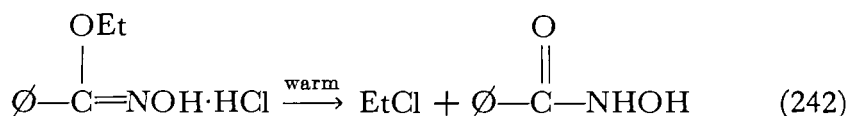


SALT AND COMPLEX FORMATION Hydroxamic acids and those derivatives that are acidic form isolable alkali metal and silver salts normally. Acidic ammonium salts of the type $2\text{RCONHOH} \cdot \text{NH}_3$ are characteristically insoluble.²⁵⁴ With transition metal salts, hydroxamic acids form many complexes, most of which are highly colored and are thus of use in detecting the hydroxamic acid function. The burgundy-colored ferric ion complexes are particularly intensely colored and easily formed and are the most widely used for test purposes. It has been observed that complex formation requires the hydroxylamine oxygen to be unsubstituted, although the nitrogen may bear a substituent. This and much other evidence indicates the hydroxamate anion is a bidentate ligand and forms complexes in which the metal ion is bound to both oxygens by chelation. The insoluble green cupric hydroxamates, for example, behave as typically covalent compounds.

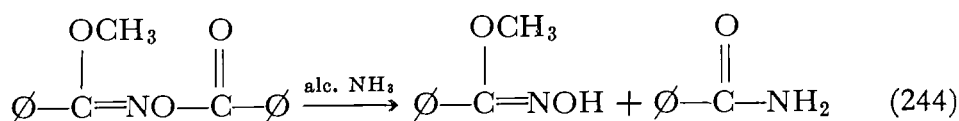
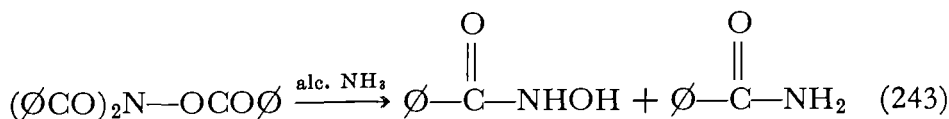


(a chelate copper hydroxamate)

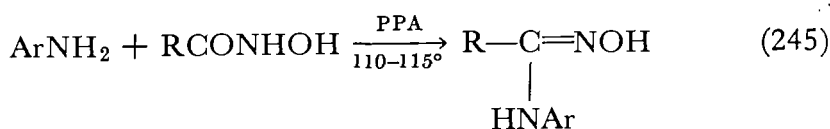
Salts of several hydroxamic acid derivatives with strong acids have been isolated in anhydrous media. Of particular interest is the behavior of the hydrochlorides of the alkyl hydroximates. In close analogy to the imidate esters, they eliminate an alkyl chloride under very mild conditions, leaving a hydroxamic acid²²⁹ (Eq. 242). The alkoximate ester hydrochlorides (type VIII) behave analogously.



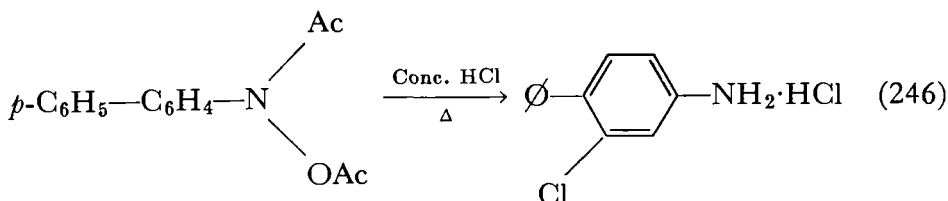
NUCLEOPHILES; HYDROLYSIS Hydroxamic acids and their derivatives are all susceptible to some extent to attack by nucleophiles, with or without auxiliary catalysis by acid or base.²⁴⁸ The hydrolysis of one acyl group from a "triacyl hydroxylamine" is quite easy; the O,N-diacyl hydroxylamines thus produced lose the O-acyl group preferentially on more severe (yet still relatively mild) treatment, and the last acyl group, in hydroxamic acids themselves, is hydrolyzed rather slowly. Stepwise removal of acyl groups from hydroxylamine can be accomplished smoothly by alcoholysis, using hydrogen chloride as catalyst,^{66b} and by ammonolysis, usually in alcohol solution²³² (Eqs. 243, 244). These processes can usually be accomplished without dislodging alkyl groups attached to the hydroxylamine moiety. Amines or phenylhydrazine are capable of cleaving



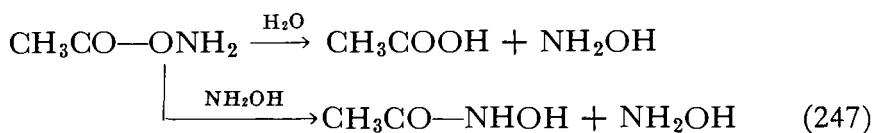
hydroxamic acids to form the corresponding amide,²⁵⁵ or of converting them to amidoximes^{245b} (Eq. 245).



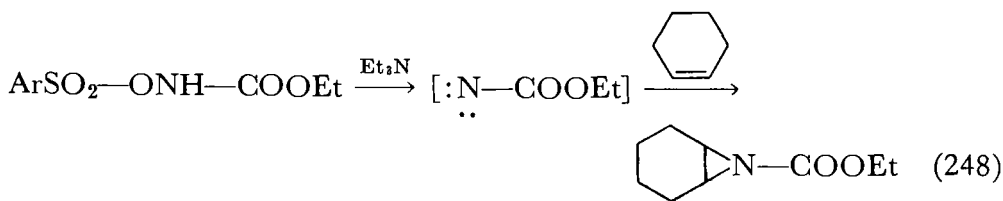
Two types of rearrangement may be encountered in solvolysis of hydroxamic acid derivatives. One of these is encountered with N-aryl derivatives with acid; chloro or hydroxy anilines are produced ^{6a} (Eq. 246) in a manifestation of the rearrangement of arylhydroxylamines discussed



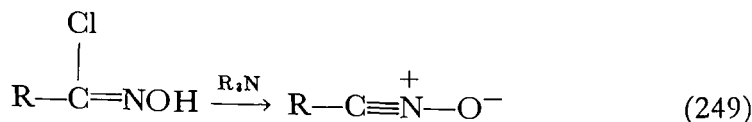
earlier in this chapter. The other is the rearrangement of O-acyl to N-acyl hydroxylamines, which actually involves hydrolysis of some O-acyl compound to give free hydroxylamine, which is then acylated by more O-acyl compound to give the N-acyl isomer and release a new molecule of hydroxylamine,²³ which propagates the process (Eq. 247).



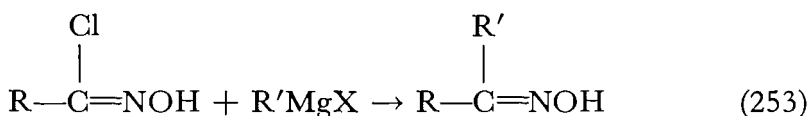
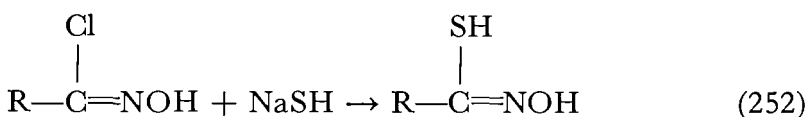
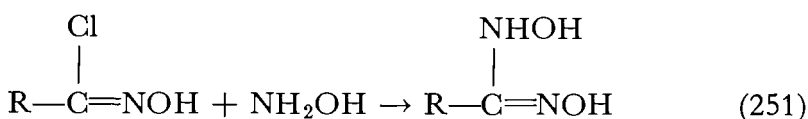
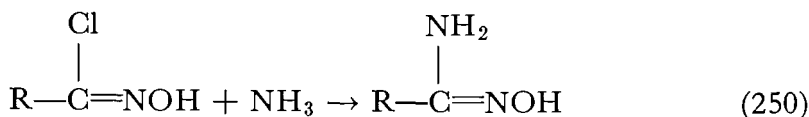
Base-catalyzed elimination has apparently been observed in a special case, that of O-*p*-toluenesulfonyl-N-carboethoxyhydroxylamine. Such a structure would ordinarily be very susceptible to Lossen rearrangement, but the presence of the very unfavorable migrating group, EtO—, apparently allows the electron-deficient intermediate EtOOC—N: to form, as evidenced by the conversion of olefins to aziridines.²⁵⁶



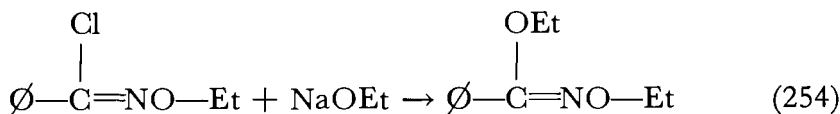
Hydroximoyl and alkoximoyl chlorides both react with various nucleophiles with replacement of the chloro by other groups; the former also undergo a competitive elimination reaction. The elimination reaction is accomplished best by alkalis or tertiary amines and leads to nitrile oxides (Eq. 249) (discussed in the next section), for which it is the most general synthesis.²⁵⁷ So easy is the elimination that hydrolysis of hydroxi-



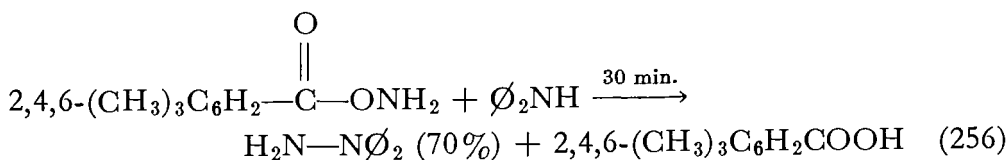
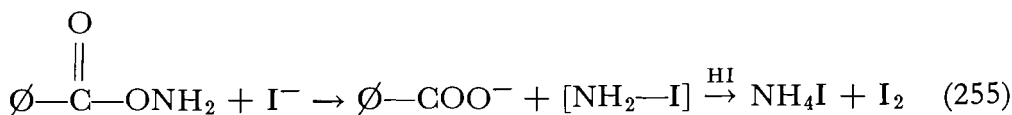
moyl chlorides to hydroxamic acids can only be accomplished with difficulty, and best by treatment with sodium or silver acetate.²³⁸ Strongly nucleophilic species, however, may give good yields of such functions as amidoximes,^{114, 238, 258} hydroxyamidoximes,^{235, 240, 259} thiohydroxamates,²⁶⁰ etc. (Eqs. 250–253). Alkoximoyl chlorides, with which elimination is not significant, undergo not only these reactions, but also react with such



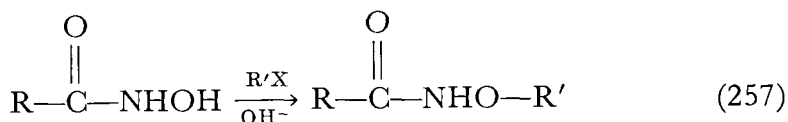
strong bases as sodium ethoxide to form alkyl alkoximates (type VIII)²³² (Eq. 254).



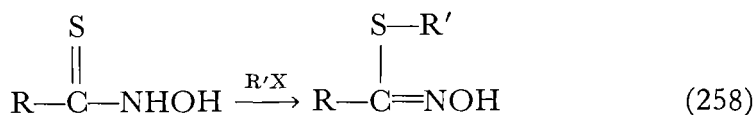
O-Acyl hydroxylamines are evidently attacked to a considerable extent by nucleophiles at the nitrogen as well as at the trigonal carbon.^{22, 261} Such a reaction, which amounts to nucleophilic displacement on a nitrogen, with RCOO^- or RSO_3^- as a leaving group, would be expected to be most favored when the nitrogen is unsubstituted and the leaving group is the anion of a very strong acid²²; various nucleophiles may take part (Eqs. 255, 256).



ALKYLATION There are abundant examples to illustrate the generality that alkylation of hydroxamic acids and derivatives in basic media occurs on the hydroxylamine oxygen (Eq. 257) if it is unsubstituted, exclusively or preferentially.^{16, 65, 66, 67, 262} The only exceptions appear to be sulfonyl hydroxamic acids, which alkylate to some extent on nitrogen,²¹⁵ and

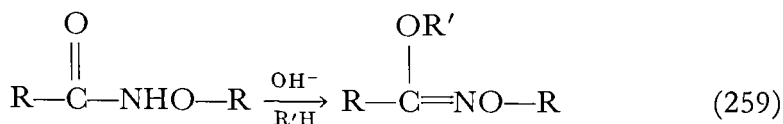


thiohydroxamic acids, which alkylate on sulfur to give alkyl thiohydroximates²⁴³ (Eq. 258). The latter situation can be attributed both to the greater nucleophilicity of sulfur relative to oxygen and to the reduced

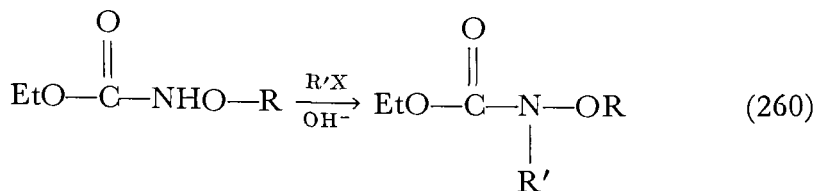


inclination of sulfur to form double bonds when a suitable alternative is available. Alkylation of hydroxamic acids with diazomethane in the absence of base produces methyl methoximates²⁶³; unfortunately, there is no evidence as to which site is alkylated first.

The second stage of alkylation, in which alkyl hydroxamates (as their alkali metal or silver salts) are treated with alkyl halides, gives results that appear to be sensitive to the type of hydroxamic acid. Fatty acid and benzoic acid derivatives without question alkylate predominantly if not entirely on the carbonyl oxygen, producing alkyl alkoximates (type VIII) in good yield (Eq. 259). The structure of the products has been ade-

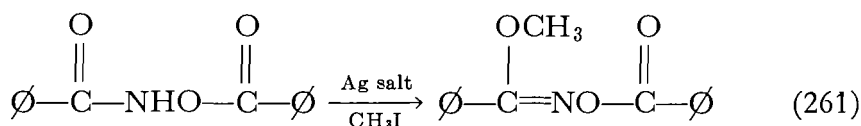


quately established by independent synthesis from alkoximoyl chlorides and sodium alkoxides, from alkyl hydroximates and alkyl halides, and by hydrolysis, which yields alkoxyamines and not O,N-dialkylhydroxylamines.^{226b, 229} Alkyl alkoxyformohydroxamates (N-alkoxyurethans), however, have been demonstrated in some variety to alkylate at least principally on nitrogen (Eq. 260). Indeed, this reaction is the basis of a

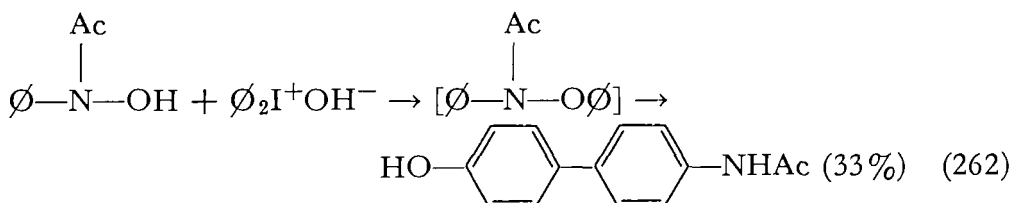


widely used synthesis of the O,N-dialkylhydroxylamines derived from them by hydrolysis.^{66, 72} This manifestation of selectivity in ambident anion alkylation appears not to have been studied further.

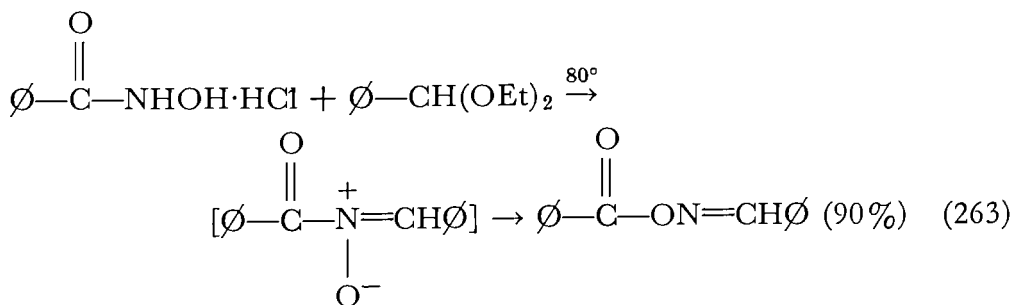
O,N-Diacyl hydroxylamines have been somewhat less extensively studied. Examples of alkylation of alkali metal or silver salts have been reported^{229, 232}; all follow the path of attack on the oxygen of the amide carbonyl, producing alkyl acyloximates (type XVI), as shown by their partial hydrolysis to alkyl hydroximates and regeneration from the latter by reacylation.



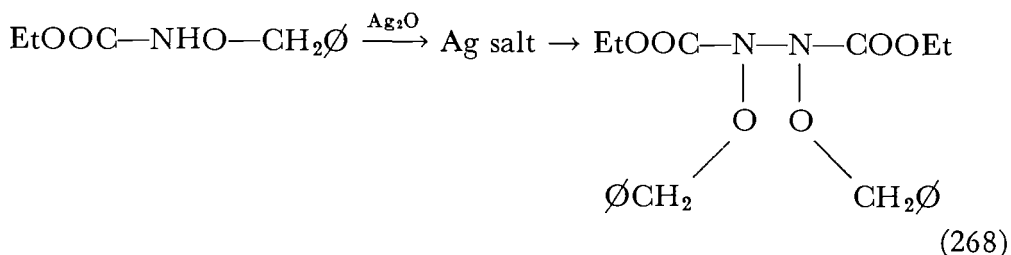
ARYLATION Arylation of hydroxamic acids has been accomplished with arylodonium salts^{68a, 264} and with aryl halides bearing activating groups such as nitro.^{68b} Substitution takes place on the hydroxylamine oxygen. In a case where arylation would have produced an O,N-diaryl derivative, the interesting discovery was made that the isolated product corresponded instead to the result of a hydroxylamine analog of the benzidine rearrangement²⁶⁴ (Eq. 262).



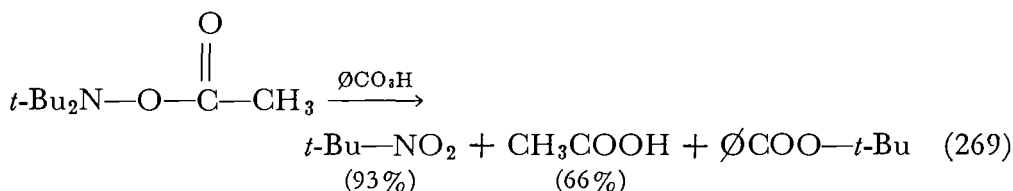
ALDEHYDES AND KETONES Aldehydes and ketones do not ordinarily react with hydroxamic acids. Reaction has been induced, however, by use of acetals. N-Acyl nitrones are presumably produced at first, but rearrange under the reaction conditions to the O-acyl isomers, or act as acylating agents toward unchanged hydroxamic acid, producing O,N-diacyl hydroxylamines¹⁵⁷ (Eqs. 263, 264).



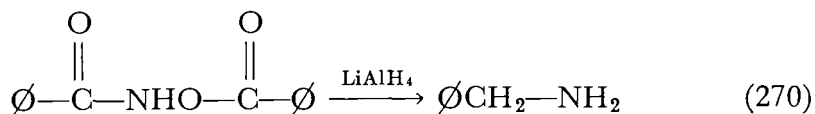
decomposition of their silver salts in ether ²⁶⁸; dimerization ensues through formation of an N—N bond (Eq. 268). The oxidation of some acyl hydroxylamines with peroxy acids has been interpreted on the basis of



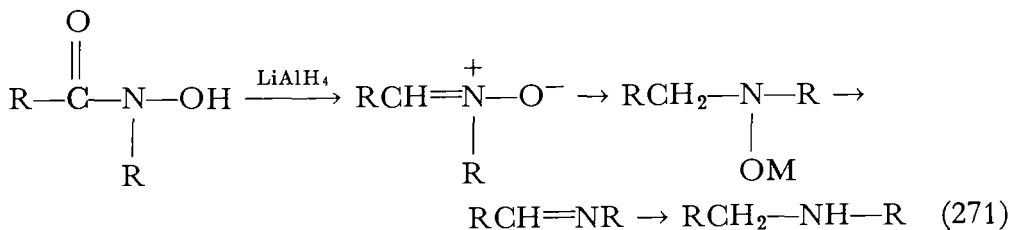
initial addition of an oxygen atom to the nitrogen to give an unstable hydroxylamine-N-oxide structure, which breaks down to give the isolated products.^{14b} O-Benzoyl-N,N-dimethylhydroxylamine yields formaldehyde, but the *tert*-butyl analog, which must behave differently owing to its lack of an α -hydrogen, gives 2-nitroisobutane (Eq. 269).



REDUCTION Reduction of hydroxamic acids by dissolving metals ²⁶⁹ or catalytic hydrogenation ^{73, 120, 270} cleaves the N—O bond and produces amides. Lithium aluminum hydride, on the other hand, eventually produces amines by complete reduction ^{157, 271} (Eq. 270). The same course is followed by O- or N-alkyl derivatives, but intermediate com-



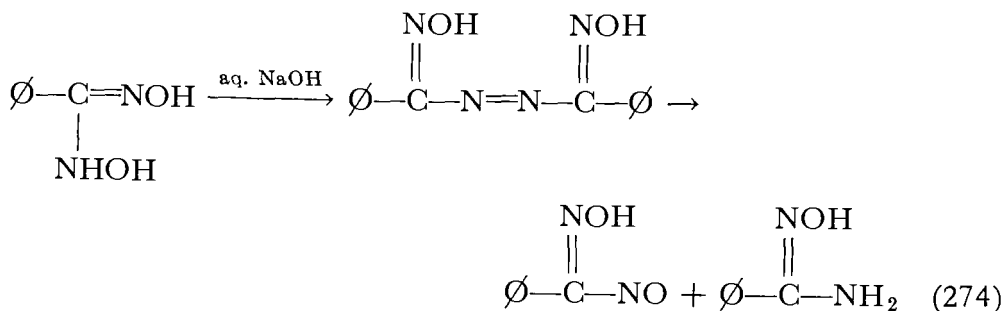
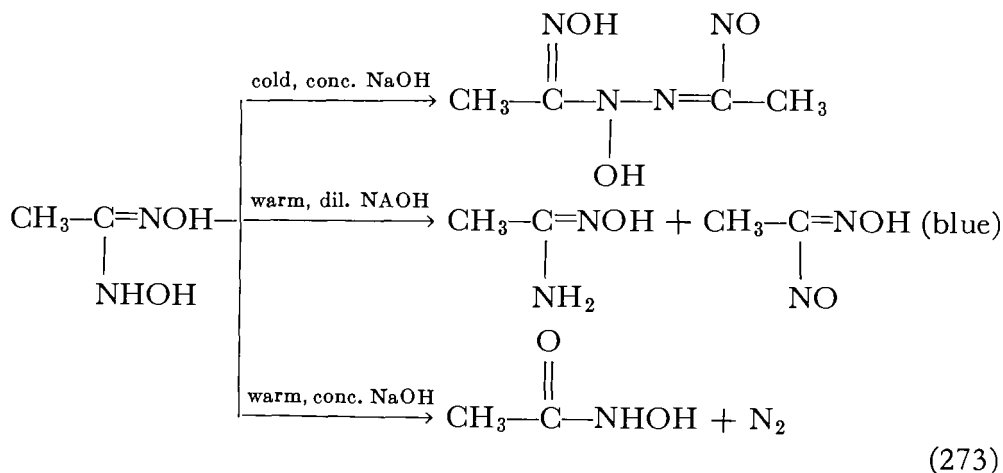
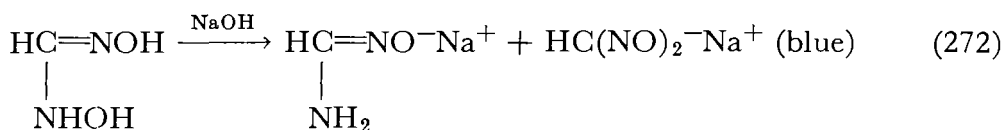
pounds—nitrones and/or hydroxylamines—can often be isolated ^{73, 120} (Eq. 271). The N,O-cleavage is believed to come about in the case of N-alkyl hydroxamic acids after reduction to the hydroxylamine stage, at



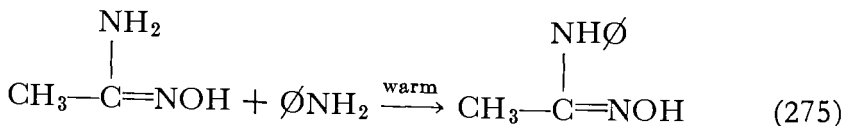
which point a metallic derivative undergoes elimination to an aldimine.

II. Compounds with Two N's (Amidoximes, etc.)²⁷²

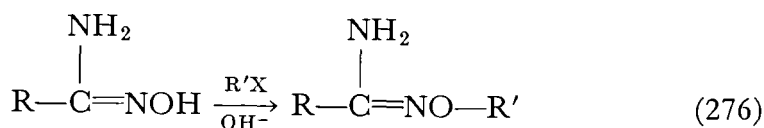
ACIDS AND BASES Amidoximes are reasonably stable substances that can be converted to hydrochlorides or to sodium salts.²³³ Transition metal salts form complexes much as do hydroxamic acids, so long as the oxygen remains unsubstituted.²³³ Hydroxyamidoximes, about which less is known, are less stable, and in the presence of strong alkali they may disproportionate into the salt of an amidoxime and of a nitrosolic acid^{235, 273} (Eq. 272). Intermediate compounds have been isolated; they have been presumed to be hydrazine derivatives (Eqs. 273, 274), but their structures are an open question. Amide nitrones (α -amino nitrones), $\text{ArNH}-\text{C}(\text{Ar})=\overset{+}{\text{N}}(\text{Ar})-\text{O}^-$, are also known.²⁷⁴



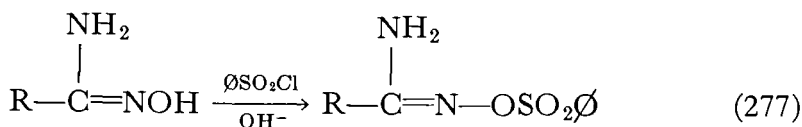
NUCLEOPHILES Hot aqueous acids hydrolyze amidoximes to the corresponding carboxylic acid. Good nucleophiles, such as aniline or hydroxylamine, replace the amino group^{273b, 275} (Eq. 275).



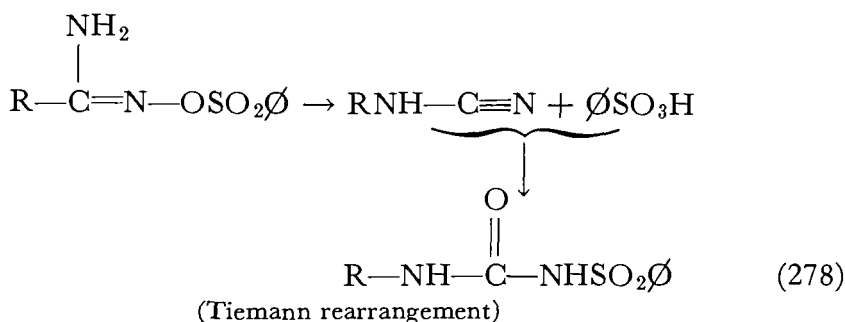
ALKYLATION Amidoximes can be alkylated in the presence of a base or as their silver salts; in either case, the alkyl group becomes attached to the oxygen ^{226b, 276} (Eq. 276).



ACYLATION Acylating agents also attack the amidoxime oxygen, ^{233, 276} giving stable O-acyl derivatives (Eq. 277). The benzenesulfonyl derivatives, however, usually rearrange when warmed in a manner closely

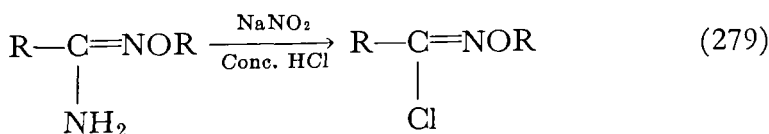


related to the Beckmann and Lossen rearrangements, to give a cyanamide



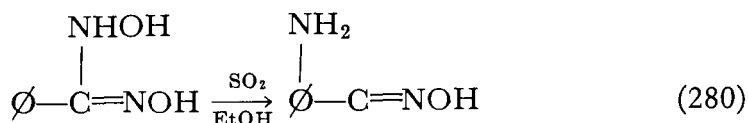
and benzenesulfonic acid, which may recombine to form a benzenesulfonyl urea ²⁷⁷ (Eq. 278). This reaction is known as the Tiemann rearrangement; it has had but little attention.^{26b} Benzohydroxyamidoxime has been reported to decompose into benzonitrile and gases on attempted acetylation.²⁷³

NITROSATION Nitrosation, by contrast, results in reaction with the amino group, although O-nitrosation as the first step is not necessarily excluded. The reaction has some of the quality of a diazotization, for when it is conducted in hydrochloric acid solution, the principal product is usually the hydroximoyl (or alkoximoyl) chloride ^{226b, 232, 276} (Eq. 279). With the use of sulfuric instead of hydrochloric acid, alkyl hydroxamates result.²⁷⁸ A case has been reported ²⁷⁵ where nitrous acid attacks the

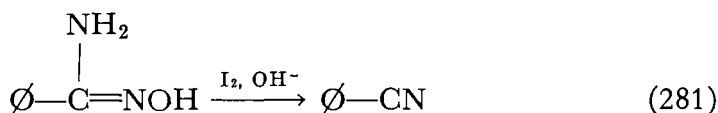


hydroxylamine nitrogen, forming an amide and nitrous oxide.

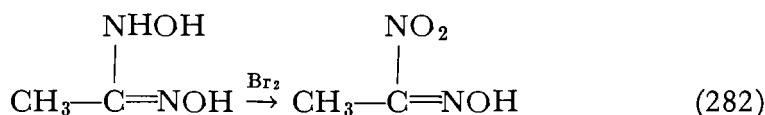
OXIDATION AND REDUCTION Amidoximes are reported to be reduced to amidines by hydrogenation over Raney nickel.²⁷⁹ Sulfur dioxide apparently does not affect amidoximes, but hydroxyamidoximes are reduced to amidoximes, perhaps through sulfamic acid derivatives²⁴⁰ (Eq. 280). The formation of benzonitrile from the oxidation of benza-



midoxime with iodine in alkaline solution (Eq. 281) is probably the result of an elimination reaction following oxidation to a 1-nitro- or 1-nitroso aldimine; with alkaline ferricyanide, an aminoöxadiazoline is reported to be formed,²⁸⁰ but the structure identification is not convincing. Oxidation of acetohydroxyamidoxime to acetonitrolic acid has



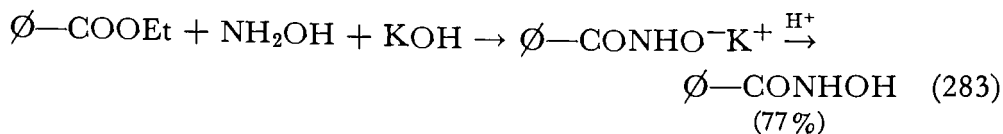
been reported²⁸¹ (Eq. 282).

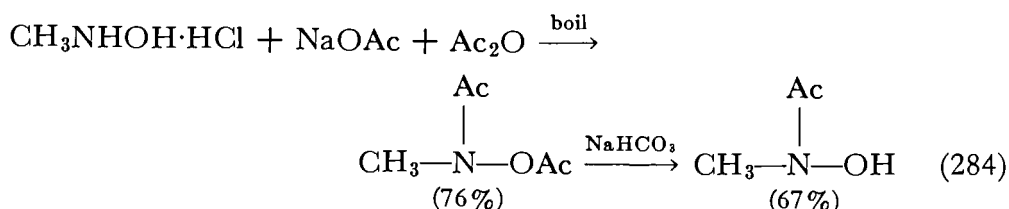


PREPARATIVE METHODS

Many carboxyl derivatives of hydroxylamines are transformation products of one another, so that the preparation of one is a reaction of another. Because of this, many preparative methods have already been described in this chapter and need not be repeated. For the most part, only those preparative methods that begin with other classes of compounds will be taken up here.

HYDROXAMIC ACIDS Hydroxamic acids are most commonly made by acylation of hydroxylamine.^{221, 245b, 249a, 282} Although all the usual acylating agents—chlorides, anhydrides, etc.—are successful, the most widely used are esters, which react particularly rapidly in a strong alkaline medium. A salt is thereby produced, from which the hydroxamic acid must be liberated by acidification (Eq. 283). This method avoids the formation of diacyl products, which may be significant or even dominant

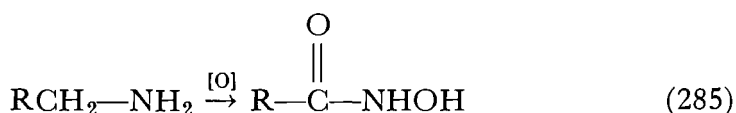




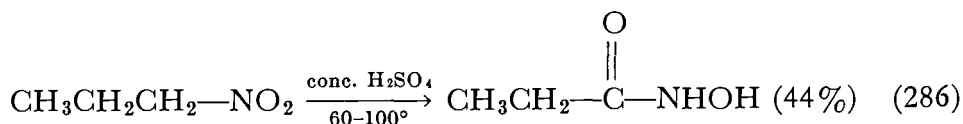
when acid chlorides or anhydrides are used (Eq. 284).^{17d} Acylimidazoles have also been used to acylate hydroxylamine.^{283a} The somewhat complicated kinetics of the base-catalyzed formation of hydroxamic acids from lactones has been carefully studied.^{283b}

O,N-Diacyl and triacyl hydroxylamines are usually prepared by acylation of hydroxylamine hydrochloride, hydroxamic acids, or their salts, with acid chlorides, anhydrides or ketenes, the degree of acylation being controlled by relative amounts, temperature, and time.^{229, 249a, 284} Stepwise acylation is also feasible, and, of course, necessary for the formation of compounds with mixed acyl groups.²²⁹

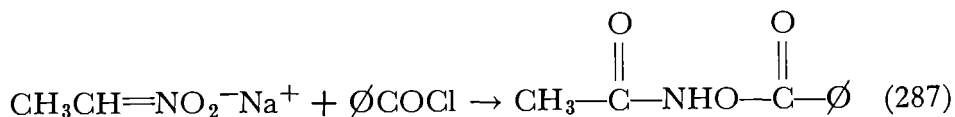
Of much narrower application are several other reactions leading to hydroxamic acids. Oxidation of primary alkyl primary amines has been used²⁸⁵ (Eq. 285). Primary nitro compounds can be caused to rearrange



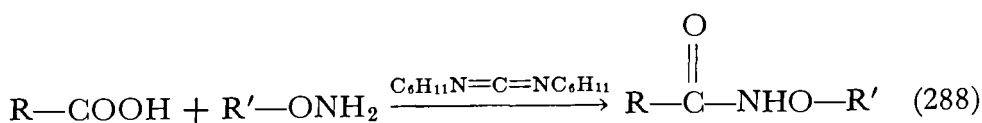
to hydroxamic acids by suitably controlled treatment with acid²⁸⁶ (Eq. 286) (cf. Chapter 14). These same compounds can be made to yield



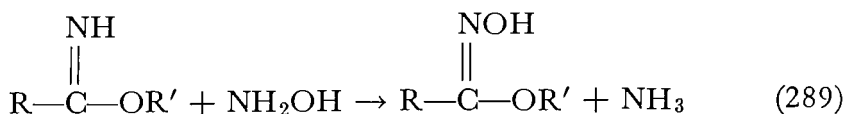
O,N-diacylhydroxylamines by treatment with acid chlorides²⁵² (Eq. 287).



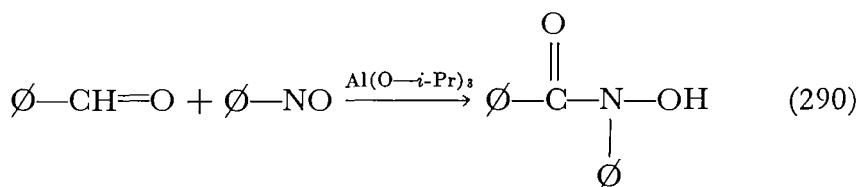
ALKYL HYDROXAMATES AND HYDROXIMATES The preparation of alkyl hydroxamates by alkylation has been discussed earlier. A useful alternative is the acylation of alkoxyamines, which can be accomplished by means of carboxylic acids and carbodiimides²⁸⁷ (Eq. 288) as well as by more conventional acylation procedures. Alkyl hydroximates are con-



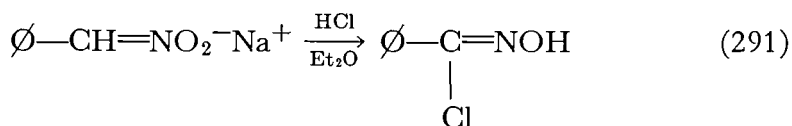
veniently prepared by the reaction of imidate esters with hydroxylamine ²³⁰ (Eq. 289).



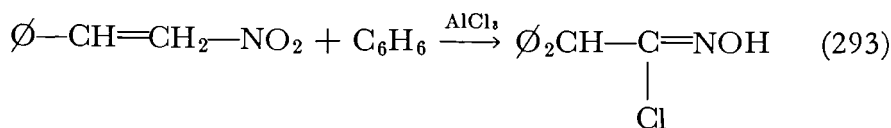
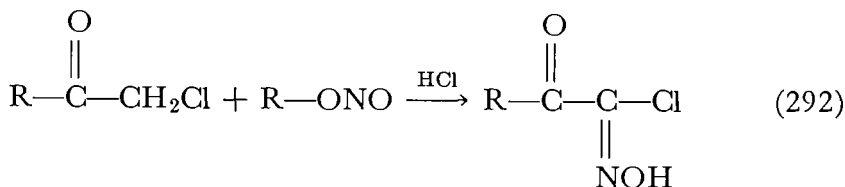
Although N-substituted hydroxamic acids are most generally prepared by acylation of N-substituted hydroxylamines, as has been mentioned in several places in this chapter, a more limited but potentially useful alternative is available in the reaction of nitroso compounds with aldehydes ²⁸⁸ under the influence of aluminum isopropoxide (Eq. 290).



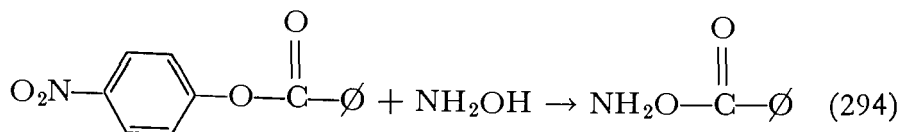
Hydroximoyl chlorides are available from the direct chlorination of aldoximes ^{185b} (Eq. 178), from the action of dry hydrogen chloride on *aci*-nitro salts ²⁸⁹ (Eq. 291), and, in more limited variety, from the nitrosation of α -chloro ketones ²⁹⁰ and the Friedel-Crafts reaction with nitro



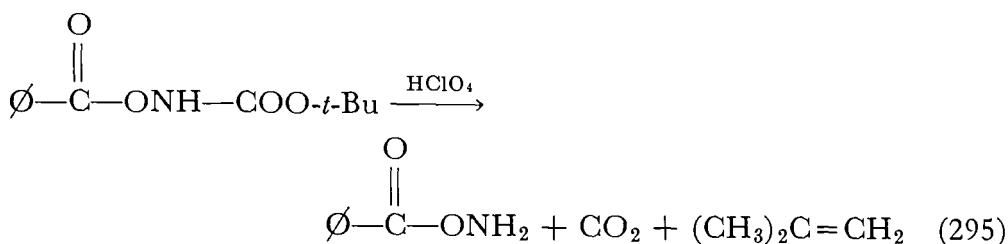
olefins ²⁹¹ (Eqs. 292, 293).



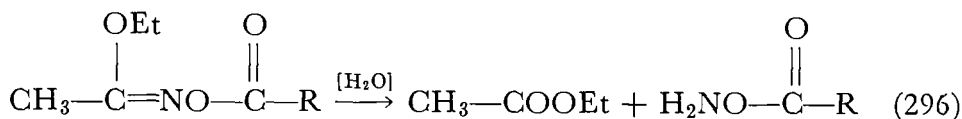
O-ACYL HYDROXYLAMINES O-Acyl hydroxylamines have been prepared by the direct acylation of hydroxylamine with such reagents as *p*-nitrophenyl benzoate ²³ (Eq. 294), by the acid-catalyzed cleavage of



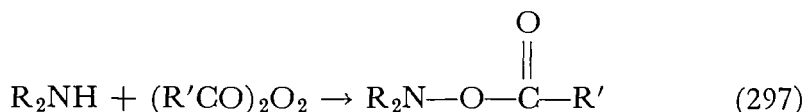
N-*tert*-butoxycarbonyl *O*-acyl hydroxylamines²⁹² (Eq. 295), by selective



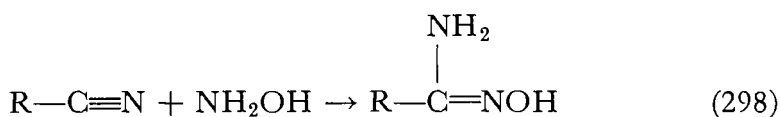
hydrolysis of alkyl acyloximates²⁹³ (Eq. 296), and by reaction of diacyl



peroxides with amines^{24, 294} (Eq. 297).

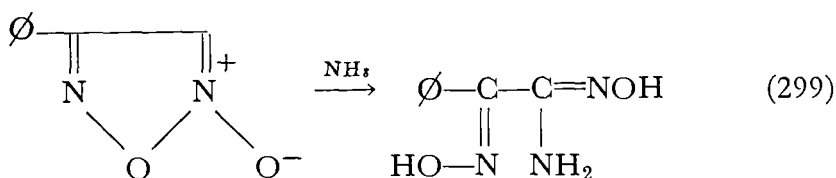


AMIDOXIMES The preparation of amidoximes can be accomplished by a variety of routes,²⁷² most of which involve nucleophilic attack on some type of carboxyl derivative. The most widely used of these is the addition of hydroxylamine to nitriles^{226b, 233, 295} (Eq. 298). Hydroximoyl

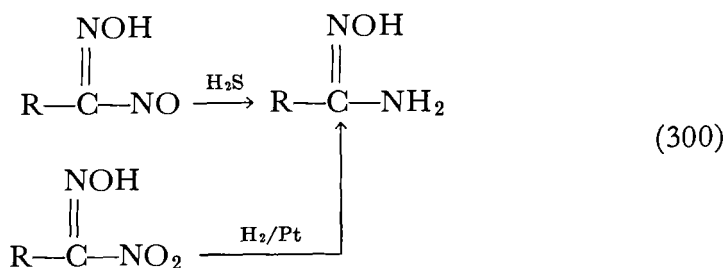


chlorides and alkyl hydroximates produce amidoximes in acceptable yields by reaction with ammonia or amines.^{114, 229, 233, 258} The inverse process, reaction of hydroxylamine with imidate esters, gives the same result.

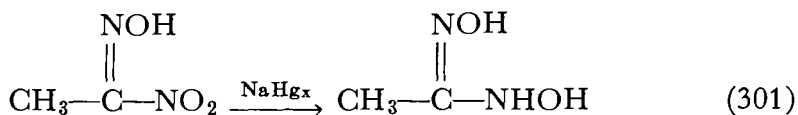
The preparation of amidoximes by ammonolysis of certain furoxans has been reported (Eq. 299); it seems not unlikely that it is actually a case of the addition of ammonia to the nitrile oxide structure.²⁹⁶ Aminolysis of hydroxamic acids by heating with amines in polyphosphoric acid is quick and convenient^{245b} (Eq. 245).



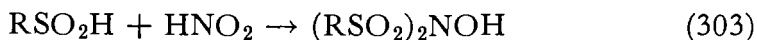
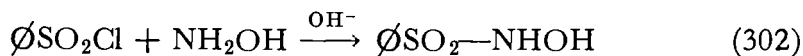
Two reductive routes to amidoximes have been reported: the reaction of nitrosolic acids with hydrogen sulfide,²⁷³ and the catalytic hydrogenation of nitrolic acids²⁹⁷ (Eq. 300).



Hydroxyamidoximes have usually been prepared by the reaction of hydroxylamine (or alkoxyamines) with hydroximoyl chlorides²⁴⁰ or with amidoximes.^{273b} The reduction of nitrolic acids with sodium amalgam also leads to hydroxyamidoximes²⁸¹ (Eq. 301).



SULFONYL DERIVATIVES Sulfonhydroxamic acids are prepared by acylation of hydroxylamine with a sulfonyl chloride^{298a} (Eq. 302); sulfonate esters behave as alkylating agents instead. Alkyl sulfonhydroxamates are prepared analogously.^{298b} *N,N*-bis(sulfonyl)hydroxylamines, $(\text{RSO}_2)_2\text{N}-\text{OH}$, can be prepared not only by repeated acylation, but also by the reaction of sulfinic acids with nitrous acid^{298c} (Eq. 303).



NITRILE OXIDES AND FULMINIC ACID

NOMENCLATURE

The substances covered in this section are compounds in which a hydroxylamine moiety is bound to *sp*-hybridized carbon: $\text{R}-\text{C}\equiv\text{N}^+-\text{O}^-$. When R is attached through carbon, the compounds are simply named by adding the separate word "oxide" after the name of the corresponding nitrile, in analogy with amine oxides. Fulminic acid is an exception, for

it is of uncertain tautomeric structure: $\text{H}-\text{C}\equiv\text{N}^+-\text{O}^-$ or $\text{C}\equiv\text{N}^--\text{OH}^+$. Derivatives in which a substituent is attached to the oxygen would be named as fulminate esters, but none is known. Nitrile oxides and fulminate esters are obviously isomeric with cyanates and isocyanates and are entirely distinct from them. Nitrile oxides were at first thought to be cyclic, and the early literature commonly considered them as heterocyclic compounds (oxazirines), although, nevertheless, using the nitrile oxide nomenclature.

PROPERTIES

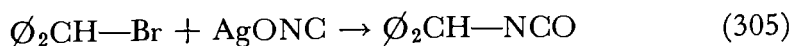
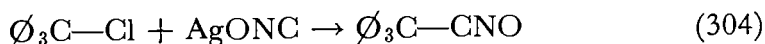
Very few nitrile oxides have been isolated, for they commonly dimerize to furoxans too rapidly. Benzonitrile oxide, however, can be obtained as an oil, insoluble in water, with a freezing point of 15° ,²⁵⁷ and several other aromatic analogs are known. Triphenylacetone nitrile oxide,^{299a} mp $153-154^\circ$, pivalonitrile oxide,^{299b} mp 18° , and acetonitrile oxide,^{299b} mp -5° , appear to be the only isolated simple aliphatic examples. Nitrile oxides do not appear to be basic.

Spectrographic data are available for many nitrile oxides that are known only in solution, as well as for those that have been isolated. The $\text{C}\equiv\text{N}$ stretching frequency shows in the infrared at $2270-2300\text{ cm}^{-1}$, and is intense; a characteristic strong band at $1350-1370\text{ cm}^{-1}$ is attributed to $\text{N}=\text{O}$.^{190, 299-301}

The dipole moments of aromatic nitrile oxides are very close to those of the corresponding nitriles.³⁰² The negative end of the dipole is directed toward the oxygen, as shown by the effect of *para* substitution: $\text{C}_6\text{H}_5-\text{CNO}$, 4.00 D.; *p*- $\text{CH}_3\text{C}_6\text{H}_4-\text{CNO}$, 4.58 D.; *p*- $\text{ClC}_6\text{H}_4-\text{CNO}$, 2.62 D.

Fulminic acid³⁰² is a volatile, unstable acid, known only in solution in water or ether, or in the form of salts. The salts are violently explosive and alarmingly sensitive; even sodium fulminate will detonate when only lightly touched with a glass rod.

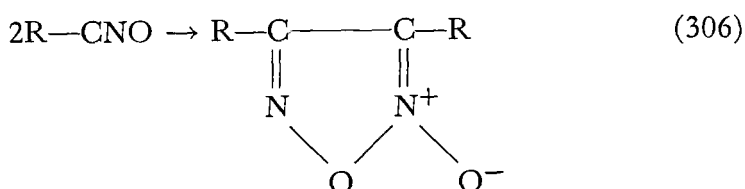
All attempts to prepare alkyl fulminates, $\text{R}-\text{ONC}$, have failed to yield an isolable substance of this nature. Triphenylmethyl chloride reacts with silver fulminate to produce triphenylacetone nitrile oxide (Eq. 304) to the exclusion of the isomeric ester,^{299a} and benzhydryl bromide reacts to give benzhydryl isocyanate³⁰⁴ (Eq. 305). The dehydrohalogenation of formalkoximoyl chlorides leads to isocyanates (as their trimers) and to oxalic acid derivatives, cyanides, and cyanates.³⁰⁵ These



facts suggest that fulminate esters may be formed, but are inherently unstable toward rearrangement, dimerization, and cleavage. The isoelectronic nitrogen analogs, R_2N-NC , by contrast, are isolable (Chapter 9).

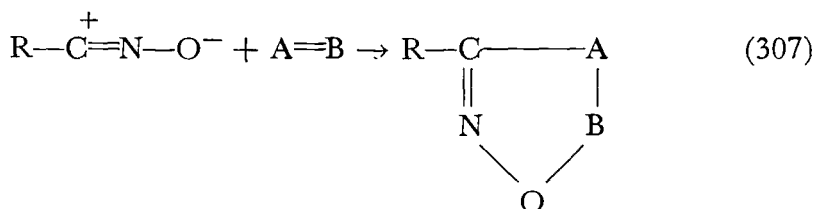
REACTIONS

Dimerization to furoxans (Eq. 306) is so rapid with most nitrile oxides that it has confined investigations to their freshly prepared solutions in the majority of cases. This self-addition is but one example of the many



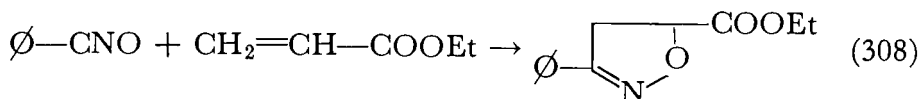
additions that nitrile oxides are capable of undergoing and that dominate their chemistry.¹⁵⁵ Such reactions are called 1,3-dipolar additions and lead to the formation of five-membered rings derived from the three

atoms of the 1,3-dipolar compound (in the present case, $R-\overset{+}{C}=N-O^-$) and two atoms originally joined by a double or triple bond, such as are found in olefins, acetylenes, carbonyl compounds, nitriles, etc. (Eq. 307).



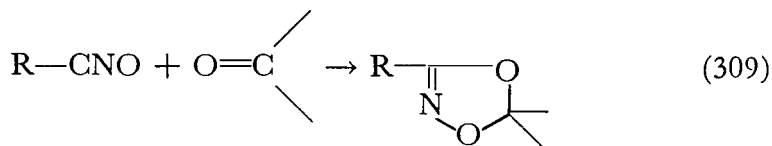
The addition of nitrile oxides to olefinic double bonds is fairly rapid, even at room temperature, but must, of course, always compete with self-addition to form furoxans. Since nitrile oxides are usually generated *in situ* by the addition of bases to hydroximoyl chlorides, it is an easy matter to limit the rate of formation of the nitrile oxide by slow addition of base, so that a high concentration, which favors self-addition, is continually avoided. In this way, yields of isoxazolines from addition of olefins have been raised as high as 100%.^{155a} A large variety of olefins have been studied, principally with benzonitrile oxide, by Quilico and his students.³⁰⁶ Although the structure of every adduct has not been rigorously established, the evidence justifies the generalization that the

oxygen of the nitrile oxide will be found in the isoxazoline attached to

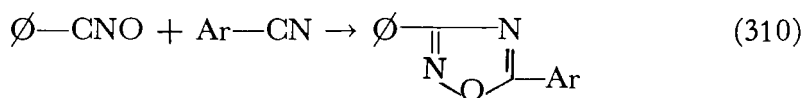


the most highly substituted carbon of an unsymmetrical ethylene (e.g., Eq. 308). Acetylenes give rise to isoxazoles.³⁰⁷

Addition to carbonyl and thiocarbonyl groups occurs to produce dioxazolines or thioxazolines, in which the nitrile oxide oxygen becomes attached to the carbonyl carbon atom³⁰⁸ (Eq. 309). Aromatic nitriles,



and aliphatic nitriles bearing electron-withdrawing groups, add analogously, forming oxadiazoles³⁰⁹ (Eq. 310).



Although the usual reaction of nitrile oxides on standing is dimerization, rearrangement to isocyanates has been observed to result from heating³¹⁰ (Eq. 311). The mechanism of this rearrangement has not been

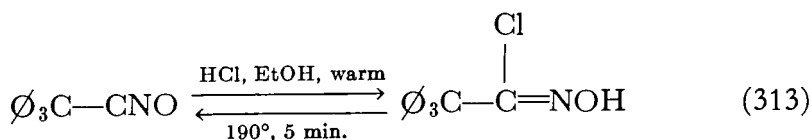


revealed, but the process is unusually interesting inasmuch as the result cannot be achieved by a simple migration of an atom or group.

ACIDS Dilute aqueous acids have no effect on nitrile oxides, but concentrated hydrochloric acid brings about hydrolysis to a carboxylic acid and hydroxylamine³¹¹ (Eq. 312). Dry hydrogen chloride adds not only

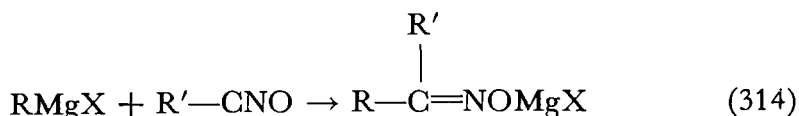


to benzonitrile oxide at 0°, but also in generally high yield to triphenylacetone nitrile oxide and many others to form hydroximoyl chlorides³¹⁰ (Eq. 313). Benzonitrile oxide has been claimed instead to form a dimer isomeric with the diphenylfuroxan commonly formed.³¹⁰ Phosphorus



pentachloride does not react with benzonitrile oxide.³¹¹

NUCLEOPHILES Many nucleophiles, such as aniline, phenylhydrazine, and hydroxide ion, have little action on nitrile oxides,^{298a} but aliphatic amines add to form amidoximes,^{299b} and mercaptans form alkyl thiol-hydroximates.^{260b} Grignard reagents add to form salts of oximes (Eq. 314).^{299a, 311}

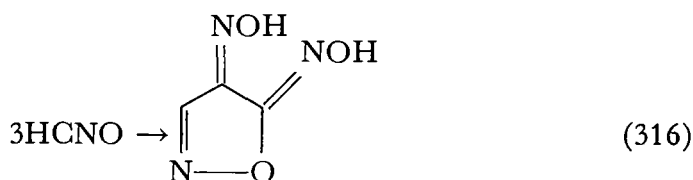


The oxygen can be removed from nitrile oxides by treatment with zinc and acid^{299a, 311} (Eq. 315). Oxidation has not been reported;

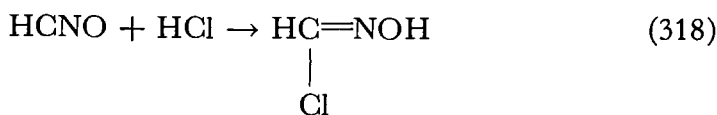
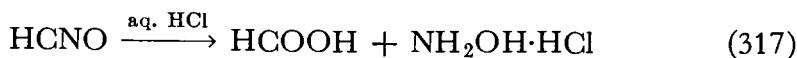


benzonitrile is reported to be inert to bromine or iodine.³¹¹

FULMINIC ACID REACTIONS Fulminic acid behaves in some ways as the simplest of the nitrile oxides and in other ways like an isocyanide. It easily polymerizes to a variety of substances, of which the simplest is a trimer, “metafulminic acid,” which is an isoxazolidinedione dioxime³¹² (Eq. 316). Hydrolysis of fulminic acid with hydrochloric acid yields



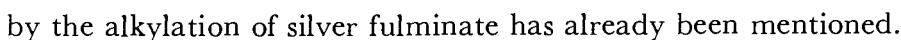
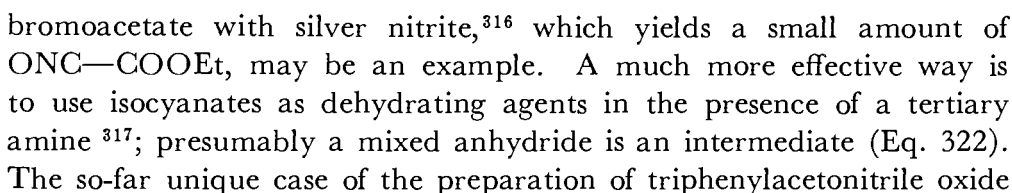
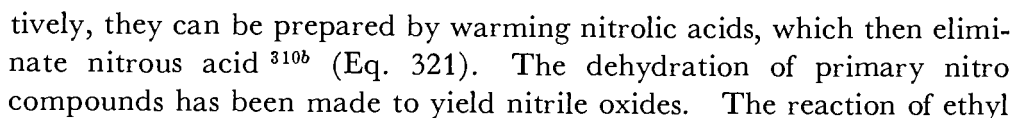
formic acid and hydroxylamine hydrochloride. Hydrogen chloride adds



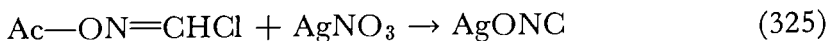
to form formohydroximoyl chloride³¹³ (Eq. 318). The addition of halogens, which gives dihaloformaldoximes in high yield,³¹⁴ is analogous to the reactions of isocyanides. The results of alkylation of fulminate salts have already been mentioned; acylation appears to be similar, for silver fulminate and benzoyl bromide give dibenzoylurea (Eq. 319), presumably derived from benzoyl isocyanate.³⁰⁴



Nitrile oxides are most commonly prepared by treating hydroximoyl chlorides (prepared by chlorinating aldoximes) with base,^{190, 301, 315} which may be sodium carbonate, alkali (Eq. 320), or a tertiary amine. Alterna-

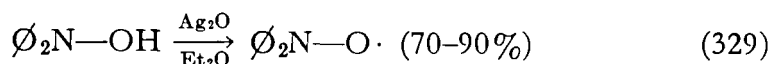


Fulminic acid can in principle be made by the same reactions that produce other nitrile oxides, and indeed, it has been prepared (as a salt) from formonitrolic acid ³¹⁸ (Eq. 323), from nitromethane ³¹⁹ (Eq. 324), and from O-acetylformohydroximoyl chloride ³²⁰ (Eq. 325). The simplest way, however, is also the oldest: the reaction of mercury and nitric acid



with ethanol. The many steps in this reaction have been shown to consist of oxidation to acetaldehyde, followed by nitrosation, oxidation, nitration,

oxidation of diphenylhydroxylamine with silver oxide under ether ³²² (Eq. 329); Tollens' reagent, ³²³ air, ^{31b} nitrogen dioxide, ³²² potassium ferri-

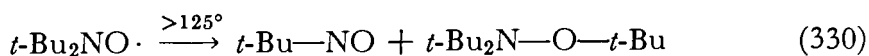


cyanide, ³²³ and sodium hypobromite ³²³ have also been used with good results with various hydroxylamines.

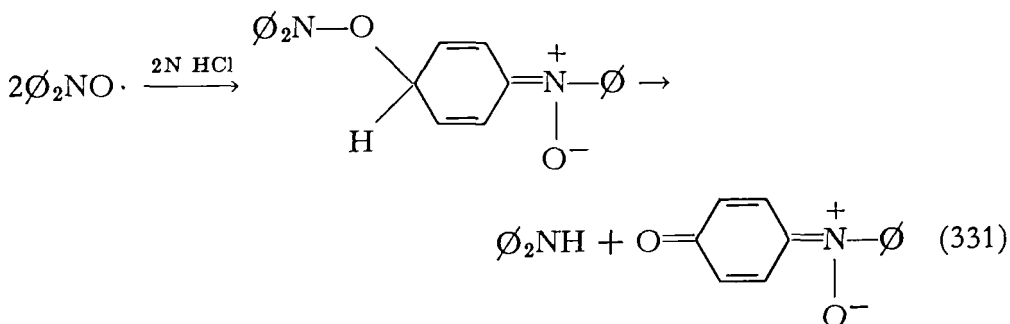
Only those nitroxides having no α -hydrogens have so far been found stable enough to isolate, although others, including monosubstituted examples, have been detected in solution by their electron-spin resonance signals. ³³ Di-*tert*-butyl nitroxide ^{31b} is a red oil that distills at 60°/11 mm.; diphenyl nitroxide ^{31a} (mp 62° dec.) and *tert*-butyl-2,6-dimethoxyphenyl nitroxide ^{31b} (mp 101–102.5°) are dark-red solids. Diphenyl nitroxide and its *p,p'*-dimethyl analog decompose in a few hours at room temperature, even in a vacuum, but other examples, such as the *p,p'*-dinitro analog, are apparently stable indefinitely. The deep red color characteristic of nitroxides results from a weak maximum in the visible spectrum (*t*-Bu₂NO·, λ_{max} 465 m μ ; log ϵ , 0.95). ^{31b} Di-*tert*-butyl nitroxide has a dipole moment of 3.08 D. ^{31b}

Monosubstituted nitroxides have been observed in alkaline solution as their anions, the anion-radicals formed by the action of certain reducing agents on nitroso compounds, ^{19c, 324, 325} or as intermediates in the action of nitric oxide on Grignard reagents. ³²⁶

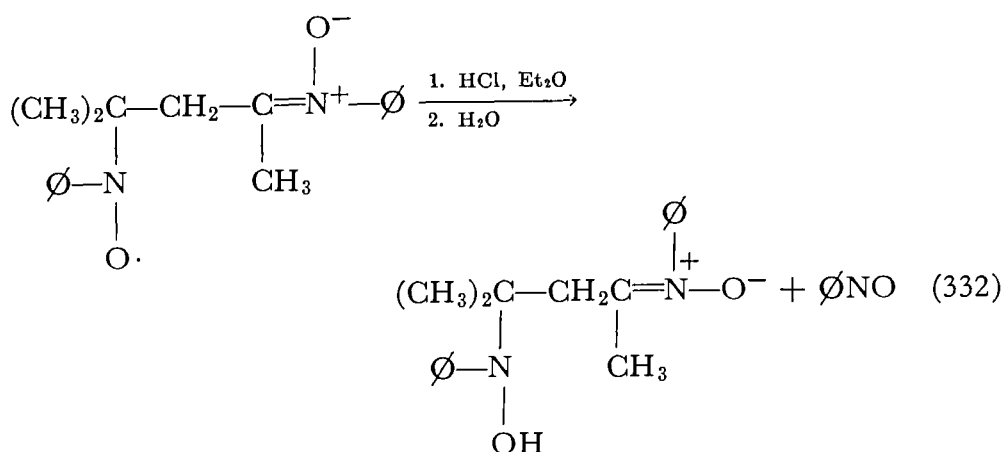
Decomposition of nitroxides, brought about by heating or contact with mineral acids, is in general a disproportionation, which, however, follows various paths. With di-*tert*-butyl nitroxide, transfer of an alkyl group occurs ^{31b} (Eq. 330); diphenyl nitroxide instead undergoes oxygen transfer,



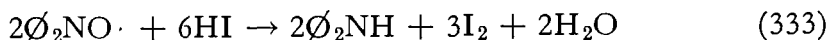
apparently by free-radical attack of one molecule on the *para* position of another, and becomes converted to diphenylamine and quinone anil N-oxide ³²² (Eq. 331). Still another mode of disproportionation is shown



by an aryl alkyl nitroxide related to mesityl oxide ³²³ (Eq. 332).

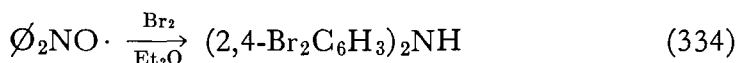


Nitroxides are readily reduced to either the parent hydroxylamine or the corresponding amine. Diphenyl nitroxide liberates iodine quantitatively from dilute hydriodic acid ^{31a} (Eq. 333), but this ability is evi-

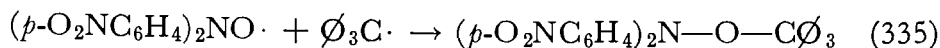


dently not general, for di-*tert*-butyl nitroxide can be prepared by the oxidizing action of iodine.^{31b} Simple reduction to the hydroxylamine stage has been accomplished with phenylhydrazine³²² and with aluminum amalgam in moist ether.³²³ Sodium borohydride does not reduce di-*tert*-butyl nitroxide.^{31b}

The fleeting character of the nitroxides bearing an α -hydrogen is apparently in part due to their susceptibility to further oxidation to nitrones.³³ Di-*tert*-butyl nitroxide is cleaved by oxidizing agents to *tert*-nitrosobutane and isobutene, however ^{31b}; this reaction may actually be the source of the *tert*-nitrobutane obtained from the oxidation of N,N-di-*tert*-butylhydroxylamine with peroxybenzoic acid. Bromine, on the other hand, works in part reductively (through released HBr?) on diphenyl nitroxide, converting it to 2,2',4,4'-tetrabromodiphenylamine ^{31a} (Eq. 334).

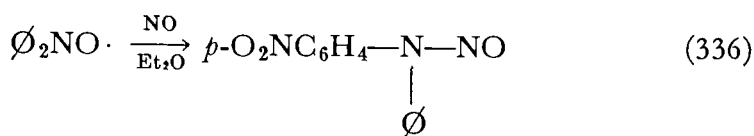


The nitroxides are quite reactive toward other free radicals, even though they do not themselves dimerize. Diaryl nitroxides react almost immediately with triphenylmethyl, forming O-substituted hydroxylamines ³²¹ (Eq. 335). This type of reaction is apparently the last step



in the formation of trisubstituted hydroxylamines from the action of free radicals on nitroso compounds.³²⁷ Nitric oxide also reacts rapidly. The

compound isolated from diphenyl nitroxide is not the simple adduct, but the result of rearrangement and nitrosation³²² (Eq. 336); the product



from di-*p*-tolyl nitroxide has been shown to be of a different kind, but has not been further identified.³²² Nitrogen dioxide produces nitro diaryl nitroxides or nitro diarylamines.³²²

Alkylidene nitroxides,¹⁸⁸ $\text{R}_2\text{C}=\text{NO} \cdot$, have been detected in solution, and imidoyl nitroxides, $\text{ArC}(=\text{NAr})\text{—N}(\text{Ar})\text{—O} \cdot$, derived from amide nitrones, are isolable.²⁷⁴

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chapter
nine

Hydrazine Derivatives

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ALKYL AND ARYL HYDRAZINES

NOMENCLATURE

Alkyl and aryl hydrazines are named where possible by naming the attached groups and using "hydrazine" as a suffix, as in "isopropylhydrazine," $(\text{CH}_3)_2\text{CHNHNH}_2$, and "*p*-tolylhydrazine," $p\text{-CH}_3\text{C}_6\text{H}_4\text{-NHNH}_2$. When it is necessary to use a prefix for the hydrazine function, the form "hydrazino" is used, as in "hydrazinoacetic acid," $\text{H}_2\text{NNHCH}_2\text{-COOH}$. The presence of two or more substituents requires the use of locants; many chemists prefer to use N and N' for their graphicness, but the numbers 1 and 2 are specified in the I.U.P.A.C. rules and are used by *Chemical Abstracts*. It is often convenient to use the prefixes "*sym*"

(symmetrical) and “*unsym*” for disubstituted hydrazines, as in $\text{CH}_3\text{-NHNHCH}_3$, which may be called “N,N′-dimethylhydrazine,” “1,2-dimethylhydrazine,” or “*sym*-dimethylhydrazine.” N,N′-Diphenylhydrazine, $\text{C}_6\text{H}_5\text{NHNHC}_6\text{H}_5$, is usually called hydrazobenzene. Ions derived from hydrazine are best named by the I.U.P.A.C. form “-hydrazinium,”

as in “N,N,N-trimethylhydrazinium iodide,” $(\text{CH}_3)_3\text{N}^+\text{-NH}_2 \text{ I}^-$, although this name has also been used for the radical-ion $\text{R}_2\text{N-NR}_2^+$. The suffix “-hydrazonium,” in analogy with “ammonium,” is used in *Chemical Abstracts*, where hydrazine salts are indexed with uninverted names, under the name of the substituent. The use of this -onium suffix is unfortunate, because it leads to confusion with derivatives of hydrazones.

PROPERTIES

The simple aryl and alkyl hydrazines are liquids, usually possessed of a somewhat ammoniacal odor, and reasonably stable to storage if protected from free access of air. Monoalkyl hydrazines have boiling points that are high compared to amines of the same molecular weight, and even tetraalkyl hydrazines, in which there are no N-attached hydrogens for hydrogen bonding, boil appreciably higher than the analogous hydrocarbons. The boiling point of tetramethylhydrazine, 73° , for example, is 15° higher than that of tetramethylethane. Hydrogen bonding is nevertheless the major contributor to the high boiling point of monoalkyl hydrazines, for successive methylation lowers the boiling point, reaching a minimum with trimethylhydrazine (Table 9-1).

Alkylation of hydrazine lowers the base strength,¹ in contrast to the situation with ammonia, and the tetraalkyl hydrazines are the weakest of the group. Most alkyl hydrazines have base strengths lying between those of ammonia and aniline. They usually form salts with only one equivalent of acid. The tri- and tetraalkyl hydrazines with groups larger than butyl are nearly nonbasic, however, and do not dissolve even in concentrated mineral acid.² On the other hand, hydrazines share the strong nucleophilic character of the parent compound, and usually react with alkylating agents and carbonyl compounds much more vigorously than amines. Increased nucleophilicity is quite generally observed when two atoms with unshared electron pairs are adjacent. Edwards and Pearson³ have suggested that this is a result of repulsion between the electron pairs, raising the ground state energy; in the transition state for substitutions, one of these electron pairs becomes involved in bond formation with the electrophilic reagent, and the repulsion could thus be lessened.

Table 9-1 *Boiling points and base strengths of some hydrazines*

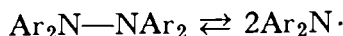
Hydrazine	bp	pK _a
NH ₂ NH ₂	113.5°	8.07
CH ₃ NHNH ₂	87°	7.87
CH ₃ NHNHCH ₃	81°	7.52
(CH ₃) ₂ NNH ₂	63°	7.21
(CH ₃) ₂ NNHCH ₃	60°/735 mm.	6.56
(CH ₃) ₂ NN(CH ₃) ₂	73°/730 mm.	6.30
C ₂ H ₅ NHNH ₂	99.5/709 mm.	7.99
C ₂ H ₅ NHNHC ₂ H ₅	85°	7.78
(C ₂ H ₅) ₂ NNH ₂	98°	7.71
C ₆ H ₅ NHNH ₂	243.5°	5.1
(F ₃ C) ₂ NN(CF ₃) ₂	32°	

A similar phenomenon is observed with hydroxylamines. A satisfactory explanation of the effect of substitution on the base strength of hydrazines has not yet been put forth, but the basicities seem to be closely related to steric crowding. Such an effect may be greater than in amines if the N—N bond distance is at all shorter than the C—N bond distances in amines, and, indeed, the N—N distance found ⁴ in both *sym*- and *unsym*-dimethylhydrazines, 1.45 Å, is apparently slightly shorter than the N—C distance, 1.47 Å, although the difference is within experimental error.

Quaternary hydrazinium hydroxides, R₃NNH₂⁺OH⁻, are strong bases, like quaternary ammonium hydroxides,^{5a} but they apparently equilibrate with the amine N-imide, R₃N⁺—NH⁻. Rearrangement to R₂N—NHR by migration of a benzyl group, if present, occurs easily.^{5b} Two N-alkyl-N-methylphenylhydrazinium compounds have been resolved into their enantiomers.^{5c}

Hydrazines show a weak acidity, too small to be observed in the presence of water, but apparently greater than that of ammonia, as shown by the ability of hydrazine, methylhydrazine, and phenylhydrazine to form sodium salts by reaction with sodium or sodium amide.⁶

Tetraaryl hydrazines show some tendency to dissociate in solution into free radicals in a manner similar to the hexaaryl ethanes.⁷ The radicals are colored, usually yellow to green, but in the crystalline state, in which



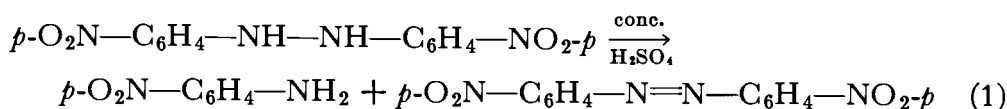
dissociation does not take place, the hydrazines are colorless. The extent of dissociation is least when there are electron-withdrawing groups, such

as nitro, in the *ortho* or *para* positions, and greatest with electron-donating groups, such as dimethylamino. The infrared spectra of alkylhydrazines resemble those of amines in the N—H stretching and bending regions.⁸

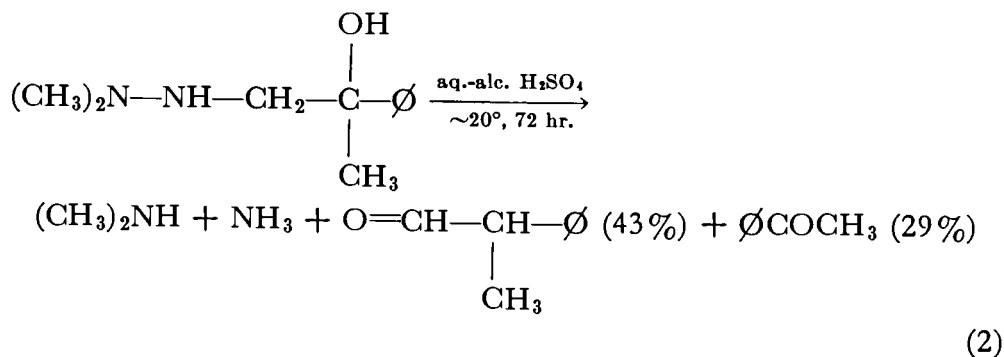
Hydrazines in general are not unusually toxic, but phenylhydrazine should be handled with care, for it can be absorbed through the skin and can cause a cumulative poisoning.

REACTIONS ⁹⁻¹²

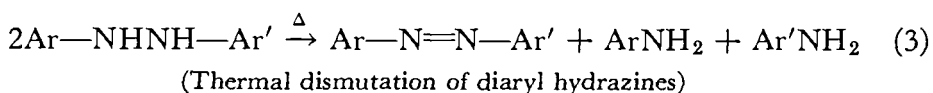
SALT FORMATION The common alkyl hydrazines are extremely hygroscopic and fume in moist air. They also absorb carbon dioxide readily, forming salts of the corresponding carbazic acid, NH_2NHCOOH . The salts of the common mineral acids are easily prepared, well crystallized, and suitable for storage. Aryl hydrazines behave similarly, but are not hygroscopic. Tertiary-alkyl hydrazines form salts normally with acids, but on warming in solution the salts easily eliminate the tertiary alkyl group, presumably initially in the form of a carbonium ion.¹³ Hydrazines with two aryl groups, especially on the same nitrogen, are often cleaved by acid into amines and oxidation products^{14, 15} (Eq. 1). *Unsym*-diphenylhydrazine requires concentrated sulfuric acid for this reaction, but *N,N*-diphenyl-*N',N'*-dimethylhydrazine is cleaved by dilute hydrochloric acid at room temperature. Some β -aminoalkyl and β -hydroxyalkyl hydrazines undergo N—N cleavage so easily (Eq. 2) that simple



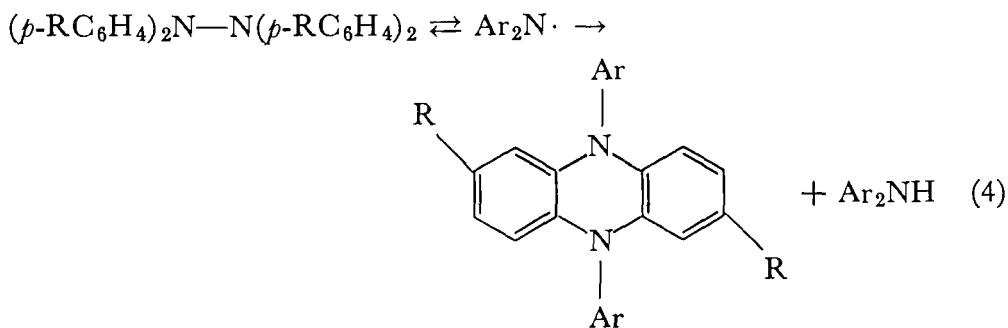
salts cannot ordinarily be prepared¹⁶; there are scattered reports of cleavage of other alkyl hydrazines under more drastic conditions.^{17, 18}



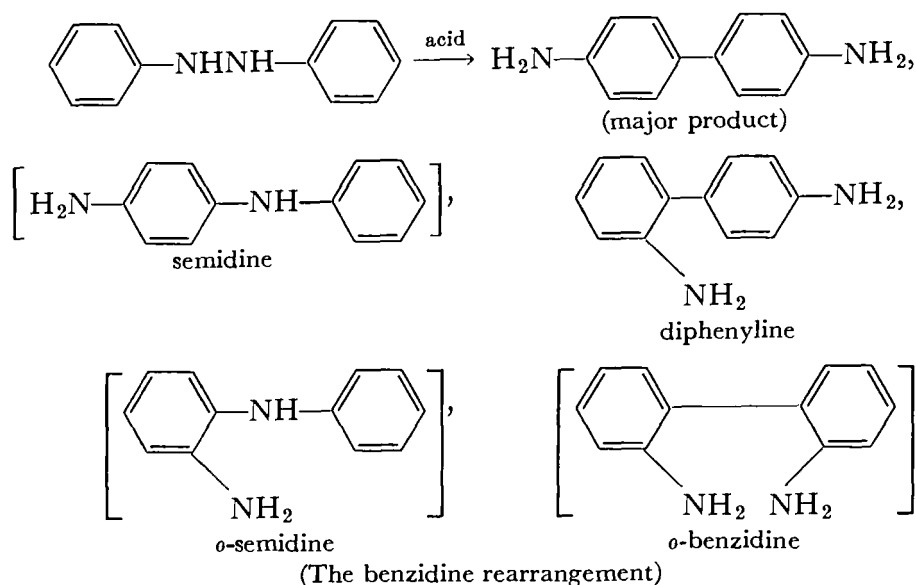
HEAT Hydrazines are in general reasonably stable to heat and can be distilled. *Sym*-diaryl hydrazines (hydrazobenzenes) are decomposed slowly by heating, however. The principal reaction is dismutation,^{14, 15} in which half the material is oxidized to an azo compound and half is reduced to amine (Eq. 3). This process cannot occur through initial dissociation into amino radicals, for hydrazobenzenes with two different aryl groups produce only the corresponding azobenzene and no symmetrical product. The same reaction apparently occurs with phenylhydrazine at its boiling point, but instead of the azo compound $\text{O}=\text{N}=\text{NH}$, its expected decomposition products, benzene and nitrogen, are obtained. Hydrazobenzenes also undergo the benzidine rearrangement when heated (see later).¹⁹



Tetraaryl hydrazines undergo a special type of decomposition slowly on standing in solution, rapidly when heated, resulting from dissociation into $\text{Ar}_2\text{N}\cdot$ free radicals.⁷ A form of dismutation occurs, in which half the hydrazine is reduced to diarylamine, and the other half is converted to a 9,10-dihydro-9,10-diarylphenazine if the *para* positions are substituted (Eq. 4), or to *p*-phenylenediamine polymers, otherwise. Tetraalkyl hydrazines, which do not dissociate into radicals, do not show this sort of reaction and are more stable to heat and storage.



BENZIDINE REARRANGEMENT The N,N' -diaryl hydrazines (hydrazobenzenes) are exceptional in that they are very sensitive to acids; although salts, such as dihydrobromides, can be isolated from nonpolar solvents,²⁰ aqueous acids usually cause the benzidine rearrangement to take place.²¹ The rearrangement is so named because the major products, *p,p'*-diaminobiphenyls, are known as benzidines, but four other types of products may also be formed: diphenylenes, semidines, *o*-semidines, and *o*-benzidines



(5)

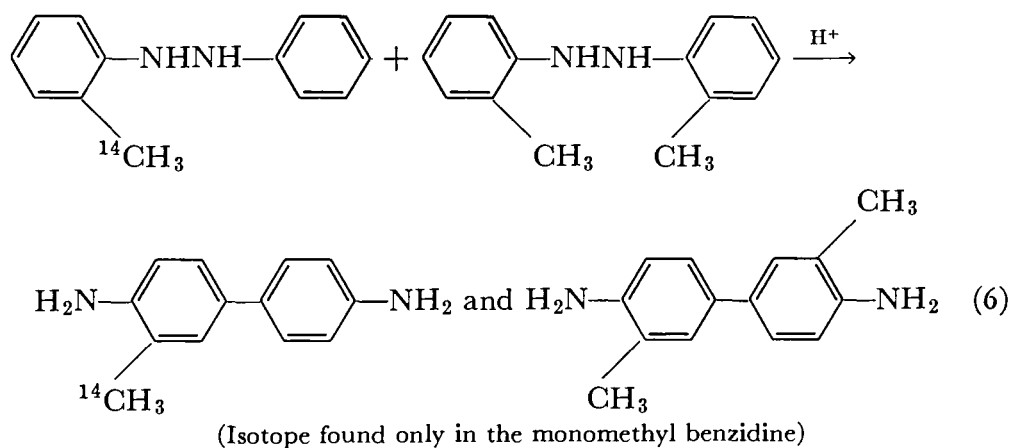
(observed only with naphthylhydrazines) (Eq. 5). Hydrazobenzene itself gives only benzidine and diphenylene, in a ratio of 3:1. The proportions of the products may vary somewhat with conditions as well as with substitution. Although blocking a *para* position generally diverts the reaction from rearrangement in favor of disproportionation to amine and azo compound,^{7b} it sometimes happens that the interfering substituent is simply expelled, allowing the rearrangement to occur normally. Substituents on the nitrogen atoms do not interfere, however, and even tetraaryl hydrazines undergo the benzidine rearrangement^{14b}; it is apparently essential only that at least one aryl group be on each nitrogen. N-Acetylhydrazobenzene rearranges normally to monoacetylbenzidine, but the N,N'-diacetyl compound does not rearrange until an acetyl group has been hydrolyzed off.

The effect of structural changes in determining the predominant product from the rearrangement of a given hydrazobenzene may be determined by recourse to three rules proposed by Dewar^{21b}:

1. The normally preferred order of products is benzidine > diphenylene >> semidine.
2. A diphenylene is the main product only from hydrazobenzenes in which the ring attached to the more basic nitrogen has a free *para* position; it is formed by linkage from this position to an *ortho* position of the other ring.
3. If a semidine is formed, the ring originally attached to the more basic nitrogen bears the primary amino group.

For the purpose of these rules, the relative basicities of the two nitrogens in a hydrazobenzene are deduced from those of the corresponding anilines. As examples of application, *p*-chlorohydrazobenzene rearranges chiefly to a diphenylene (2,4'-diamino-5-chlorobiphenyl), but *p*-methylhydrazobenzene, in which it is the substituted ring that is attached to the more basic nitrogen, gives chiefly an *ortho*-semidine (2-anilino-*p*-toluidine). It should be borne in mind, however, that these rules do not apply to hydrazonaphthalenes, which give mainly *ortho*-benzidines.

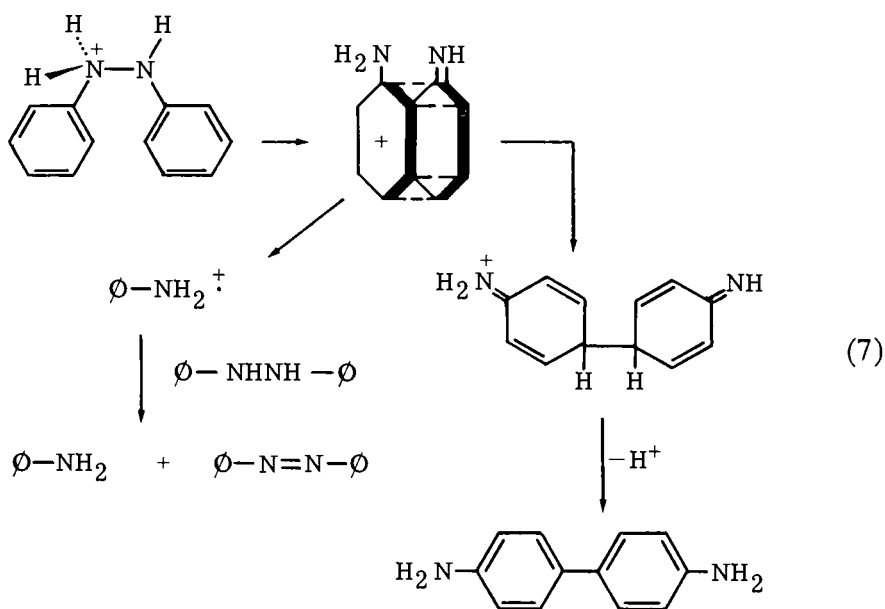
The mechanism²¹ of the benzidine rearrangement has been an object of attention for decades. It has been established that the reaction is intramolecular by experiments with unsymmetrical hydrazobenzenes, which produce only the corresponding unsymmetrical benzidine, and with mixtures of differently substituted hydrazobenzenes, which produce no benzidines arising from exchange of aryl groups²² (Eq. 6). The reaction is apparently subject to specific hydrogen ion catalysis,²³ contrary to the earlier belief in general acid catalysis. The dependence of the rate on acidity follows H_0 rather than concentration and is in most



instances close to second order at higher acidities, drifting to first order as acidity decreases.²⁴ These facts speak strongly for the existence of parallel paths of rearrangement, one through the mono-cation, one through the di-cation. At an earlier time, however, when the available evidence favored general acid catalysis, it was convincingly argued that the addition of the second proton must be rate controlling, rather than occurring as a prior equilibrium.^{21b} A pronounced kinetic isotope effect, in which substitution of deuterium oxide for water as the solvent doubles the velocity of the reaction that is first order in acidity and quadruples that that is second order, also implies normal, complete protonation prior to the transition state.²⁴ Deuteration of the ring positions of hydrazobenzene, however, affects neither the rate nor the product ratio,²⁵ from which one can conclude that the loss of the protons from carbon at the

new ring juncture occurs not only after the rate-determining transition state, but also after the product-determining steps.

Current views of the mechanism of the benzidine rearrangement have in common the concept that the molecule folds up so that the two aromatic rings are aligned face to face (Eq. 7). The resulting intermediate has been variously held to be a pair of cation radicals held in a solvent cage, or a π -complex derived from the species ArNH_2 and ArNH^+ , or ArNH_2 and ArNH_2^{++} . By localization of a C—C bond between the 4 and 4' positions, followed by unfolding and loss of protons from the same positions, benzidine is formed. The other types of products can



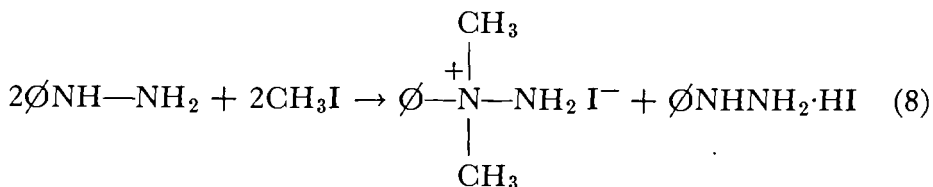
(π -complex mechanism through mono-cation)

be accounted for if it is assumed that bond localization may also occur at the 2,2' positions, and that rotation or displacement of one ring with respect to the other may occur in the complex also to allow bond localization at the 2,4' positions or from C to N. Disruption of the complex (however it may be constituted) may give rise to separate cation radicals, which lead to disproportionation products.²⁶

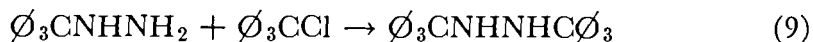
The thermally induced benzidine rearrangement¹⁹ has not been so thoroughly investigated. The distribution of products is in general different from that of the acid-catalyzed reaction, and the mechanism may well be different.

ALKYLATION Alkylation of hydrazines can be accomplished easily with the usual alkylating agents, such as alkyl halides and sulfates. With small alkyl groups, such as methyl, alkylation takes place on the

substituted nitrogen only and usually continues until the quaternary ion, $R_3NNH_2^+$, is formed.^{5a} This fact was for a long time assumed to be a result of an increase in base strength (paralleled by nucleophilicity) at the alkylated nitrogen atom, but the discovery that alkylation actually reduces the base strength of hydrazines made such an explanation inadequate. Furthermore, the same result is observed with phenylhydrazine¹ (Eq. 8), contrary to earlier reports, as well as methylhydrazine.



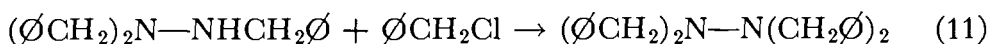
tert-Butylhydrazine²⁷ is also alkylated almost entirely on the substituted nitrogen by methyl iodide, and only when steric crowding becomes very great, as with such a group as triphenylmethyl (Eq. 9), or when re-



duction of base strength is pronounced, as with *unsym*-diphenylhydrazine¹⁴ (Eq. 10), does alkylation take place completely on the unsubstituted



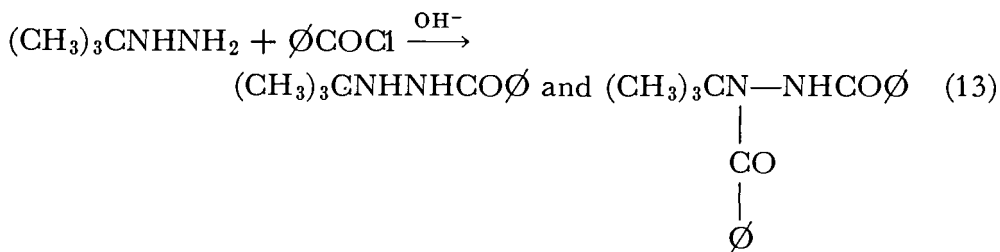
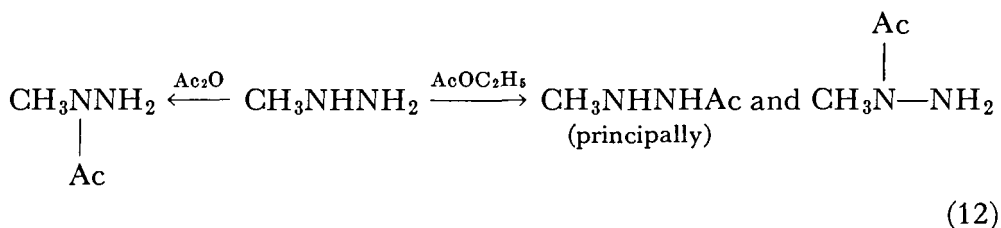
nitrogen. Alkylating agents of intermediate size often balk at putting a third alkyl group on the same nitrogen, however, and *N,N,N'*-trialkyl and *sym*-tetraalkyl hydrazines may be formed instead (Eq. 11). In such



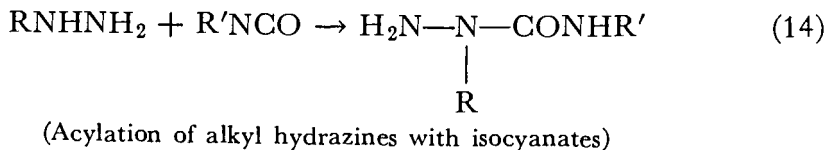
cases, alkylation at the substituted nitrogen occurs to the largest extent with alkyl iodides and least with chlorides.² This is explained by the probable fact that the length of the growing carbon-nitrogen bond in the transition state is greatest with a good leaving group, such as iodide, with the result that the transition state is looser and not so subject to destabilization by steric crowding. Arylation is apparently similar to alkylation, for it has been shown that methylhydrazine reacts with 2,4-dinitrochlorobenzene at the substituted nitrogen, whereas in the more hindered cases of *unsym*-dimethylhydrazine and picrylhydrazine, arylation occurs at the unsubstituted nitrogen.^{28, 29}

ACYLATION Acylation of hydrazines somewhat resembles alkylation, in that an alkylated nitrogen is often preferred to an unsubstituted one, but the process seems to be much more sensitive to steric crowding. The usual products from the acylation of phenylhydrazine are *N'*-phenyl hydra-

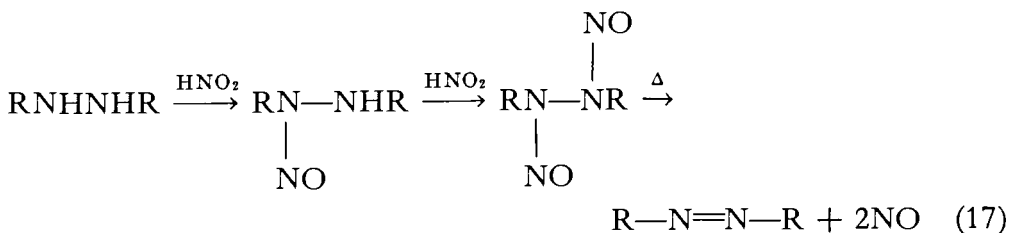
zides, $\text{RCO—NHNH—}\emptyset$, and N,N' -diacylphenylhydrazine, but the smaller monoalkyl hydrazines may be acylated at either nitrogen, according to conditions. Most interesting differences are observed in the acylation of alkylhydrazines with anhydrides and esters³⁰; anhydrides attack the substituted nitrogen, whereas ordinary esters attack the unsubstituted one predominantly (Eq. 12). Dithio esters acylate the substituted nitrogen unless the ester or the hydrazine bears a bulky group. This is probably the result of the requirement of a tighter transition state with ordinary esters, making the reaction more sensitive to steric crowding. As the size of the acyl group increases, the minor fraction of acylation at the substituted nitrogen diminishes still further. Even acid chlorides may prefer to acylate an unsubstituted nitrogen when the groups concerned are bulky, and in intermediate cases, mixtures are produced²⁷ (Eq. 13). Monosubstituted hydrazines are easily acylated twice under Schotten-Baumann conditions.



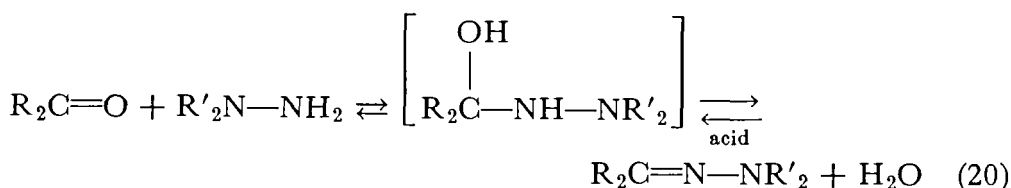
Cyanic acid, phenyl isocyanate, and phenyl isothiocyanate acylate the substituted nitrogen atom of methylhydrazine and even of isopropylhydrazine, giving 2-alkyl semicarbazide derivatives (Eq. 14).



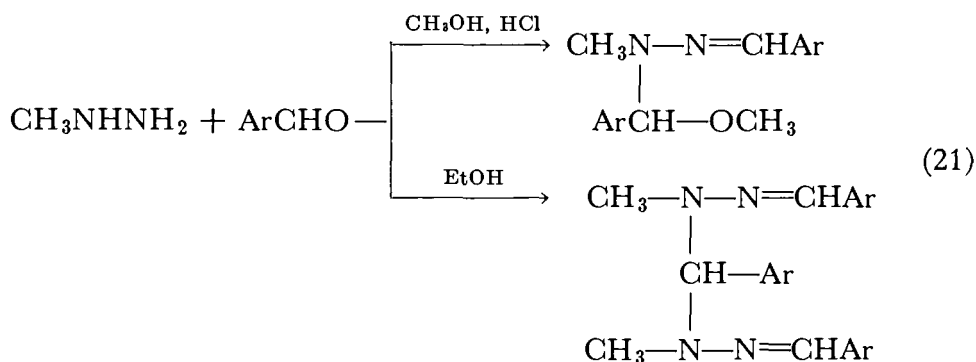
NITROSATION Nitrosation is a special case of acylation, for the nitroso group is unusually labile and may wander to a site other than the one to which it first becomes attached, especially under the influence of acid. Alkyl hydrazines, such as benzylhydrazine, apparently become nitrosated at the substituted nitrogen atom, giving RN(NO)NH_2 , whose structure is supported by the fact that they react with ketones to form

$$\begin{array}{c} \text{\O NHNH}_2 \xrightarrow{\text{HNO}_2} \text{\O N}-\text{NH}_2 \xrightarrow[\text{H}^+]{?} [\text{\O NHNH}_2\text{NO}]^+ \xrightarrow{\Delta} \text{\O}-\text{NH}_2 + \text{N}_2\text{O} \\ | \\ \text{NO} \\ \downarrow \text{H}^+ ? \\ \left[\begin{array}{c} \text{\O}-\text{N} \diagup \text{NH}_2^+ \\ | \\ \text{N}-\text{OH} \end{array} \right] \rightarrow \text{\O}-\text{N}_3 + \text{H}_2\text{O} \end{array} \quad (15)$$
$$\text{R}_2\text{NNH}_2 + \text{HNO}_2 \rightarrow \text{R}_2\text{NH} + \text{N}_2\text{O} \quad (16)$$


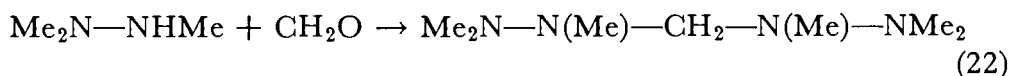
Chlorides of sulfur acids and phosphorus acids, both organic and inorganic, react with hydrazines in much the same way as other acylating agents.³⁵ Thionyl chloride gives thionylhydrazines, $\text{RNH}-\text{N}=\text{SO}$. Since sulfonyl hydrazides are easily cleaved into sulfinic acids and oxidation products of hydrazines, such hydrazides cannot always be isolated



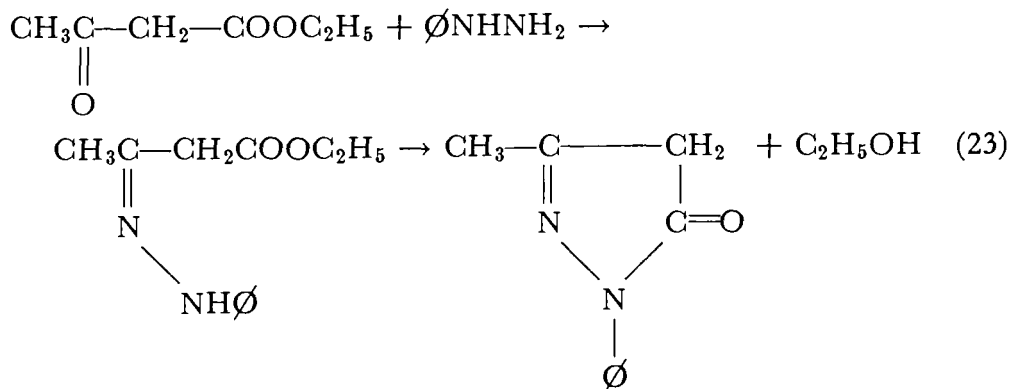
Hydrazone formation occurs without complication with aryl, acyl, and *unsym*-dialkyl hydrazines, but monoalkyl hydrazines can react with more than one mole of aldehyde, condensation occurring at the substituted nitrogen atom as well as the unsubstituted one ⁴⁰ (Eq. 21). *Sym*-Disubstituted, tri- and tetrasubstituted hydrazines do not ordinarily react with

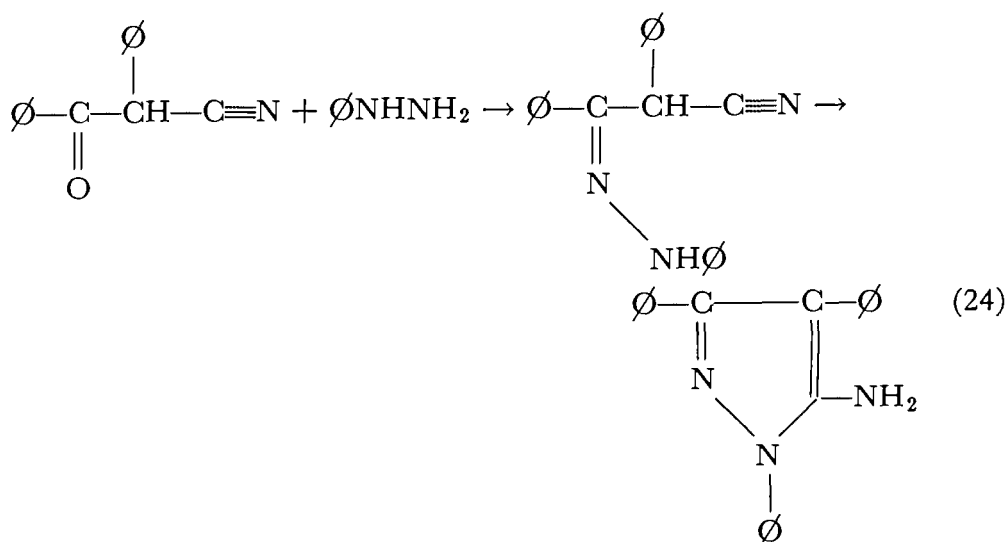


aldehydes and ketones, although *gem*-dihydrazines are formed in some cases ^{41, 42} (Eq. 22).

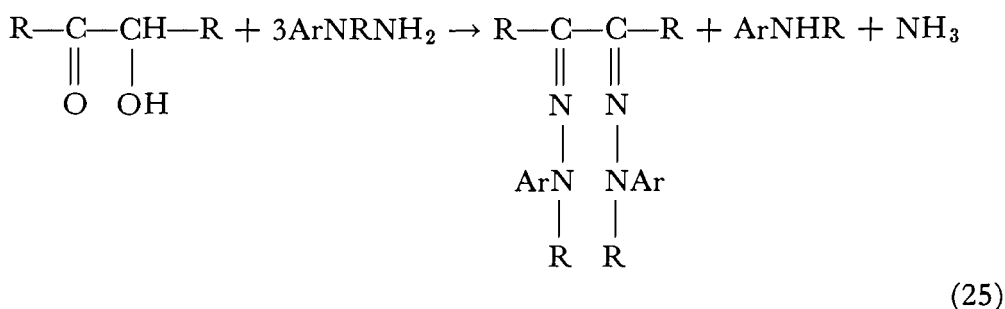


The presence of other functional groups adjacent to a carbonyl group can greatly affect the nature of the ultimate product by making secondary reactions possible. β -Dicarbonyl compounds, such as acetoacetic ester, apparently undergo normal hydrazone formation as a first step, but the intermediate hydrazones often undergo cyclization so easily (Eqs. 23, 24) that they have not been isolated. Reactions of this sort are of great synthetic importance in the chemistry of pyrazoles.

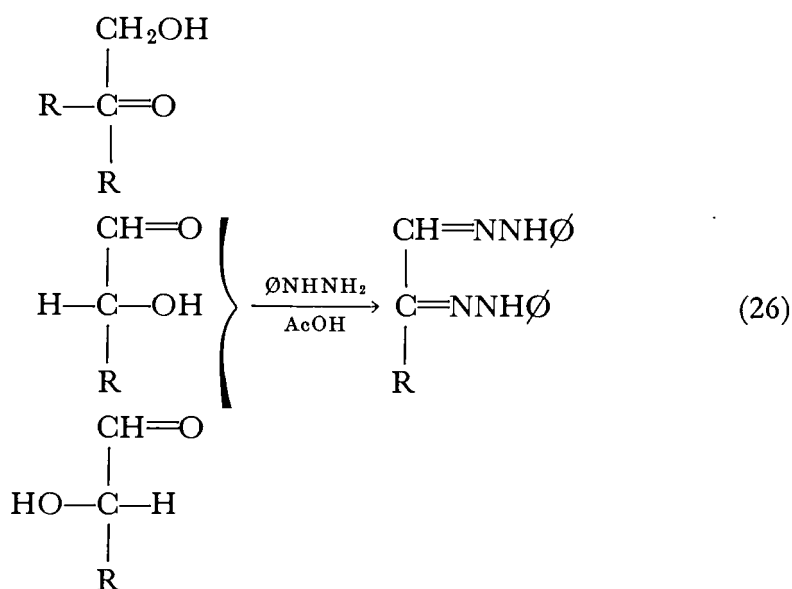




The most important secondary reaction between hydrazines and polyfunctional ketones and aldehydes is undoubtedly that leading to osazones. It occurs in general when an α -hydroxy ketone or aldehyde is treated with an excess of a monoaryl or N-aryl-N-alkyl hydrazine; three moles of hydrazine are consumed, of which two are incorporated into the osazone (a *bis*-hydrazone of an α -diketone), and the third serves as an oxidizing agent, becoming reduced to ammonia and an aniline (Eq. 25).

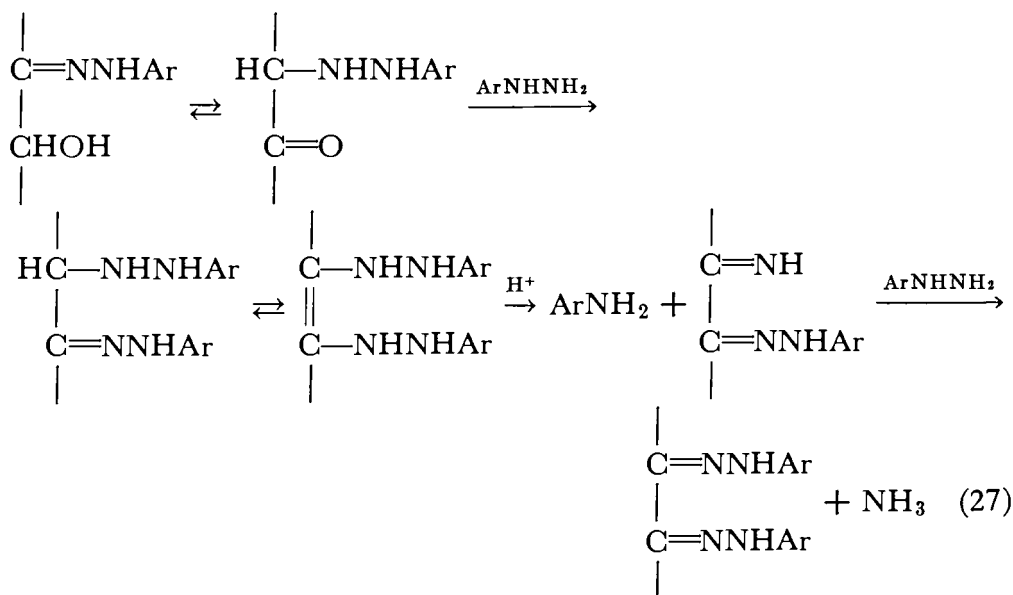


OSAZONES Osazone formation has received enormous application in sugar chemistry. By means of this reaction, Emil Fischer was able to unravel most of the confused skein of simple sugar chemistry and thereby to lay the foundation for modern carbohydrate chemistry. The particular value of the reaction in this field is that it yields well-crystallized, easily isolated and identified products, and destroys one specific asymmetric center if the carbon bearing the original hydroxyl group is not the end of a chain. The classic example is the proof that fructose, mannose, and glucose, which are isomeric hexoses, differ only at the 1- and 2-carbon atoms, for they all give the same osazone with phenylhydrazine (Eq. 26).



(Formation of the same osazone from fructose, mannose, and glucose)

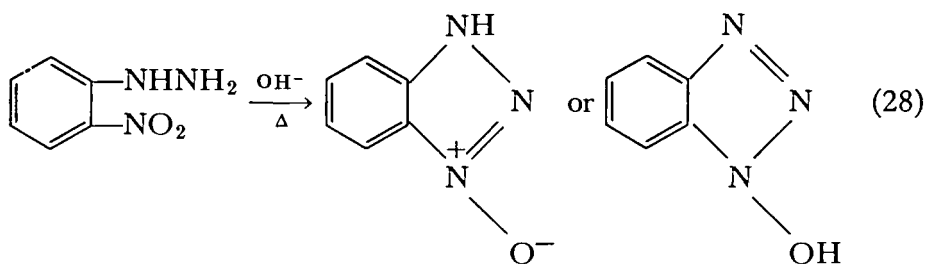
The mechanism of osazone formation has been an object of discussion and investigation for many years. The evidence suggests ^{43, 44} that the simple arylhydrazones react with a second mole of aryl hydrazine through first tautomerizing to an α -hydrazino ketone, analogous to the Amadori rearrangement of α -hydroxy aldimines to α -amino ketones. The α -hydrazino hydrazone produced then tautomerizes to an enamine structure, which undergoes an acid-catalyzed cleavage to form aniline and an imine-hydrazone, which can react with a third molecule of aryl hydrazine to form the osazone with ejection of ammonia (Eq. 27). The overall process ordinarily stops at the osazone stage even if there is still an ox-



(Probable path of osazone formation)

dizable hydroxyl group α to the osazone structure; this is perhaps because the conjugation in the osazone system retards the necessary tautomerizations. N-Methylphenylhydrazine, however, works down the sugar chain all the way to the hexahydrazone stage,^{45a} a fact which, along with other evidence, strongly suggests that unsubstituted aryl osazones are stabilized by virtue of their existence in a quasiaromatic hydrogen-bonded chelate ring form.^{45b}

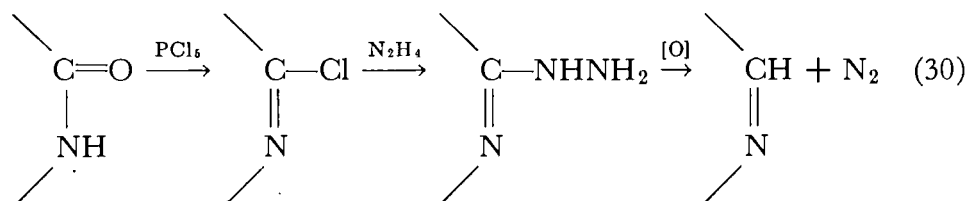
Although hydrazines do not ordinarily react with nitro groups except by oxidation-reduction, *o*-nitroaryl hydrazines undergo a condensation on heating, with loss of water, formally analogous to hydrazone formation.⁴⁶⁻⁴⁸ The familiar reagent 2,4-dinitrophenylhydrazine reacts only to a small extent in this way, however. A base is usually used as a catalyst, although it is not essential; the products are benzotriazole oxides or their tautomers, N-hydroxybenzotriazoles (Eq. 28). Nitroso compounds react with arylhydrazines to give analogous open-chain compounds, hydroxytriazenes or triazene oxides (see Chapters 12 and 13).



OXIDATION Hydrazines can act as either oxidizing or reducing agents, since their oxidation state stands between that of ammonia and that of elemental nitrogen; both behaviors are encountered in reactions, although the reducing properties are usually more pronounced. All classes of substituted hydrazines, even the tetrasubstituted, are oxidizable under moderate conditions, except the quaternary hydrazinium salts, but the ease as well as the nature of the reactions varies considerably. Even very mild oxidizing agents, such as ammoniacal silver nitrate (Tollens' reagent) and Fehling's solution, are reduced by most hydrazines, and can be used as qualitative test reagents for the hydrazine structure when other easily oxidized groups are known to be absent.

There is a difference of four electrons (or four hydrogen atoms) between the oxidation state of hydrazine and that of nitrogen. Oxidation can therefore be expected to occur in stages and the products to depend on both the quantity and the nature of the oxidizing agent. Although one-electron oxidations are well established with tri- and tetrasubstituted hydrazines, monosubstituted hydrazines usually give products resulting from two-electron and four-electron oxidations (loss of two or four hydrogen atoms). Two-electron oxidation would give rise to diimides or their

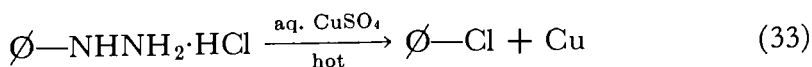
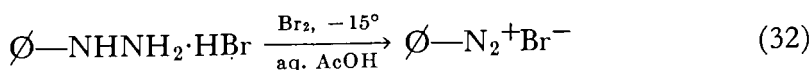
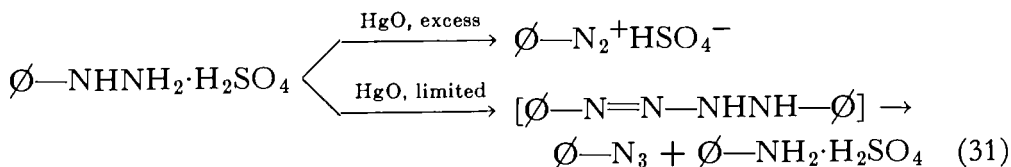
tautomers, $R-N=NH$ or $RNH=N^+$; these substances themselves have not been isolated from oxidations, but their expected decomposition products, nitrogen and a hydrocarbon, comprise the major products from oxidation of hydrazines^{28, 29, 47-49} (Eq. 29) with such varied reagents as copper sulfate, periodate, ferric chloride, ferricyanide, mercuric oxide, and oxygen, when used in appropriate quantity. The decomposition of phenylhydrazine in air, for example, gives principally benzene, along with small amounts of colored tars. This oxidation is of considerable synthetic value, for its use permits the replacement of oxygen or halogen by hydrogen, as shown in Equation 30. It has been particularly useful in the synthesis of heterocyclic parent systems, where the rings must often first be built up in amide form. So easy is the oxidation by air that



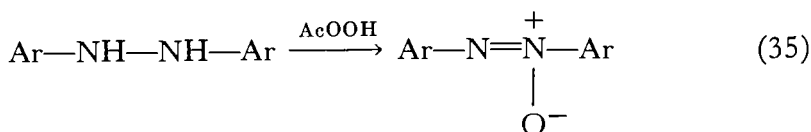
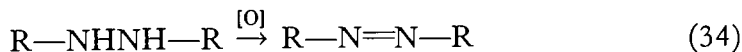
(Replacement of oxygen or halogen by hydrogen through oxidation of a hydrazine)

many aryl hydrazines have never been obtained analytically pure except in the form of derivatives. Air oxidation ("autoxidation") of hydrazines is, however, often slow unless traces of heavy metal compounds, particularly Cu^{II} , are present.⁵⁰

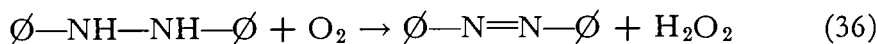
Four-electron oxidation is usually encountered with aryl hydrazines in acid solution with excess oxidizing agent. If the temperature is not too high, diazonium salts are produced.⁴⁹ These are seldom the only product, however, because even if they do not decompose, they can couple with unoxidized aryl hydrazine, producing tetrazenes⁴⁹ (Eq. 31). These in turn usually decompose into an aniline and an aryl azide. Under appropriate conditions, the usual decomposition products of diazonium salts can be obtained (Eqs. 32, 33). In view of all the possibilities for reaction, it is not surprising that the oxidation of aryl hydrazines can give very complex mixtures.



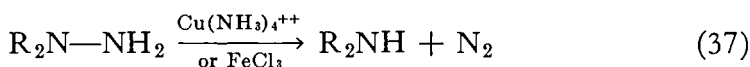
Sym-disubstituted hydrazines lose two hydrogen atoms easily, and the azo compounds produced, being reasonably stable, can usually be isolated (Eq. 34). A wide variety of oxidizing agents, including bromine, permanganate, etc., can be used. The reaction is the best method for preparing aliphatic azo compounds.⁵² With peroxyacetic acid, the oxidation can be carried all the way to azoxy compounds⁵³ (Eq. 35). Oxidation with molecular oxygen is particularly interesting, for it can give



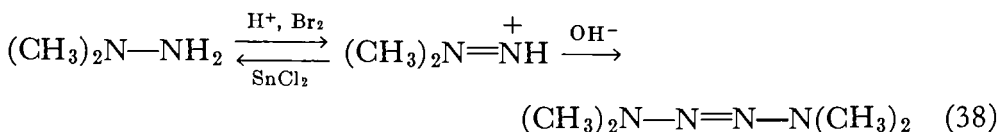
rise to hydrogen peroxide nearly quantitatively⁵⁴ (Eq. 36).

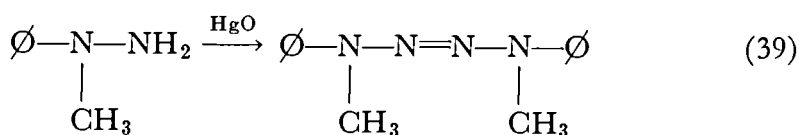


Unsym-disubstituted hydrazines also present a complicated picture in oxidation. The simplest reaction is removal of one hydrogen atom, which results in the loss of nitrogen and the formation of a secondary amine (Eq. 37). Even Fehling's solution can accomplish this, but ferric chloride or permanganate is easier to use. This reaction has value in structure proof, since the secondary amines are usually easily identified.^{28, 29}

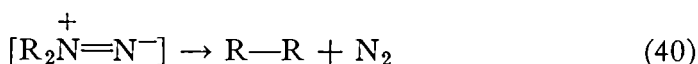


Removal of two hydrogen atoms from *unsym*-disubstituted hydrazines produces charge-separated diimides, $\text{R}_2\text{N}=\overset{+}{\text{N}}^-$ (as their salts, $\text{R}_2\text{N}=\overset{+}{\text{N}}\text{H X}^-$), called azamines, (Eq. 38), their dimers, the tetrazenes, $\text{R}_2\text{N}-\text{N}=\text{N}-\text{NR}_2$, (Eqs. 38, 39), or their decomposition products⁵⁵⁻⁶⁴ (Eqs. 40, 41). What is isolated in a given experiment depends not only on how much oxidizing agent is used, but also on the nature of the oxidizing agent and the conditions. Since the decomposition of N',N' -dialkyl sulfonyl hydrazides, which is believed to pass through the azamine stage, sometimes gives products different to those from oxidation of the corresponding hydrazine,⁶¹ it seems reasonable to attribute the distinctions to differences in the ease of formation of tetrazenes under the respective reaction conditions. It has been shown⁵⁷ that there is an optimum

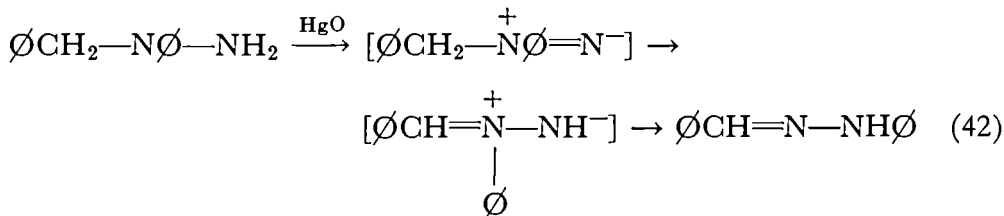




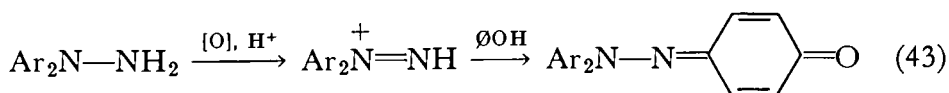
pH for tetrazone formation, which apparently requires the presence of both azamine and its cation. Tetrazenes might also be formed through reaction of the azamine with unreacted hydrazine to give an easily oxidized tetrazone.⁶⁰ Fragmentation of azamines, which apparently gives free radicals that either dimerize (Busch-Weiss reaction⁶³) or disproportionate, is favored by the presence on the α -carbons of groups that stabilize radicals or charges in the transition state. The same products are observed when azamines are generated by reduction of nitrosamines with



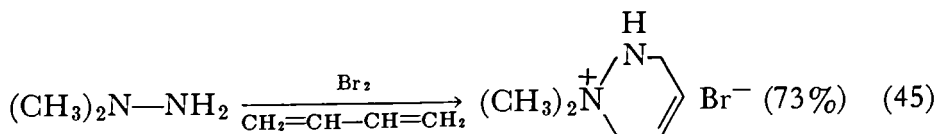
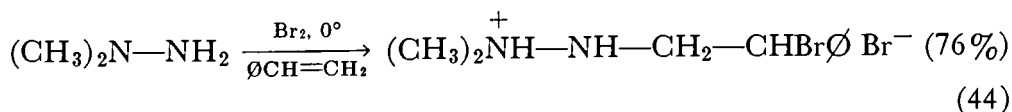
dithionite. Hydrazones have also been obtained from azamine-producing reactions⁶⁴; they presumably arise by tautomerization followed by N-to-N' migration (Eq. 42) (see section on sulfonyl hydrazines). Oxidation of hydrazines to azaminium salts in the presence of phenols or aromatic



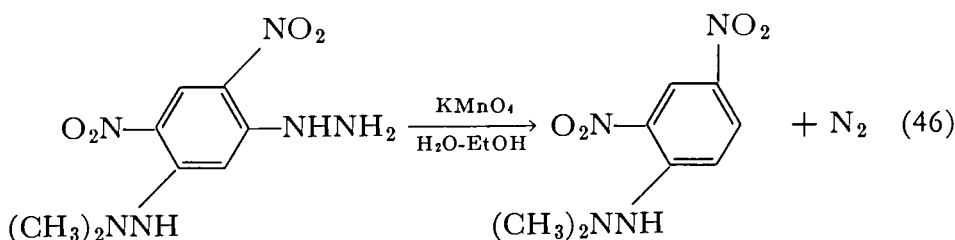
amines leads to coupling at the *para* position with formation of quinone hydrazones⁶⁵ (Eq. 43). In the presence of conjugated olefins, such as styrene or butadiene, either cyclic or linear addition may take place^{16b}



(Eqs. 44, 45). The reactions of tetrazenes are described in Chapters 11 and 12.

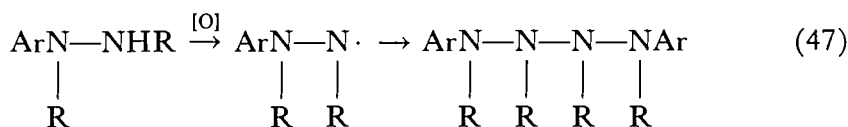


Trisubstituted hydrazines are more difficult to oxidize than mono- and disubstituted compounds and are not usually affected by Tollens' or Fehling's reagents. The difference in susceptibility to oxidation between mono- and trisubstituted hydrazines is well illustrated by 2,4-dinitro-5-dimethylhydrazinophenylhydrazine; hot, neutral permanganate affects only the NH_2NH —group, giving 2,4-dinitrophenyl- N',N' -dimethylhydrazine.²⁸ Only one hydrogen can, of course, be removed from tri-

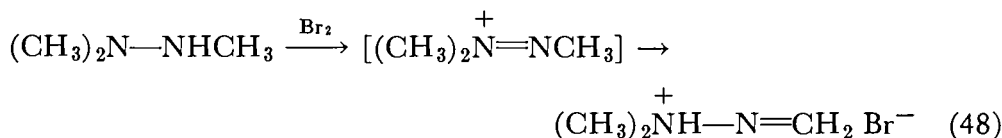


substituted hydrazines, and the immediate products are nitrogen-free radicals⁶⁶ (hydrazyls). These are formed from trisubstituted hydrazines holding at least one aryl group, but usually dimerize to form tetrazanes (Eq. 47). Certain of these dissociate reversibly into the free radicals again (see Chapter 12). A two-electron oxidation would produce a

diazonium ion, $\text{R}_2\text{N}^+=\text{NR}$; the probable rearrangement product of such

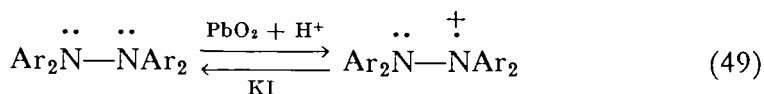


a species is formed in the oxidation of trimethylhydrazine with bromine³⁶ (Eq. 48).

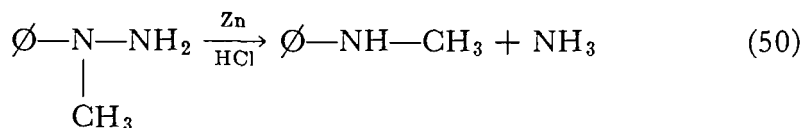


Tetrasubstituted hydrazines are even more resistant to oxidation, but tetraaryl hydrazines form a special case.³⁷ They react with certain strong oxidizing agents, such as bromine or chlorine tetroxide; one electron is removed, and the hydrazine is converted to a colored radical-ion (Eq. 49). Potassium iodide reduces it back to the hydrazine. The reaction is analogous to that of triphenylamine with the same reagents, producing the radical-ion O_3N^+ . Salts of these ions have been isolated in a number of cases, but they are usually rather unstable. They have unfortunately been called "hydrazinium" salts, a term which is also used for ordinary hydrazine salts in general, and would be the source of much

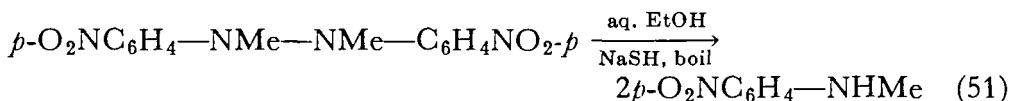
confusion were these radical ions more commonly met with; "hydrazylum" seems to be an unambiguous alternative.



REDUCTION Reduction of hydrazines of necessity cleaves the N—N bond, producing two molecules of amine ⁶⁸ (Eq. 50). It is not a rapid reaction, however, a fact that allows many hydrazines to be prepared by reductive methods. Raney nickel hydrogenation and dissolving metals in the presence of strong acid seem to be the most effective reducing agents, although magnesium in methanol has been used to reduce quaternary hydrazinium salts. Dismutation, which was mentioned earlier in this chapter is, of course, a case of self-reduction. N,N'-Bis-(*p*-nitro-



phenyl)-N,N'-dimethylhydrazine is an unusual case, in that it is reduced smoothly by sodium sulfide ¹⁵ (Eq. 51).



PREPARATIVE METHODS

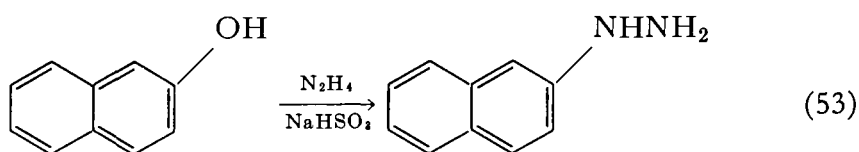
MONOSUBSTITUTED Monoalkyl hydrazines can in principle be made by direct alkylation of hydrazine^{2, 16, 30} with the usual reagents, but this method is seldom used because of the difficulty of stopping the reaction before more than one alkyl group has been introduced. The most successful example seems to be ethylhydrazine, which has been made in 32% yield by direct alkylation ⁶⁹ (Eq. 52). Attempted alkylation of



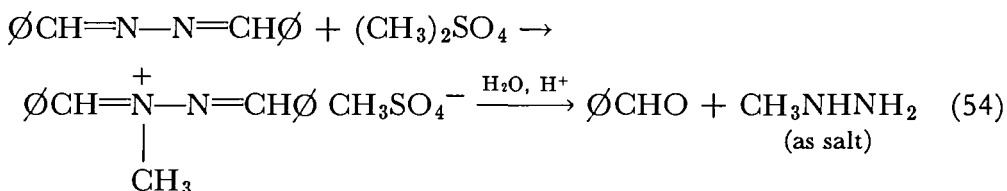
hydrazine with such compounds as bromomalonic ester and α -bromoacetoacetic ester, which contain positive halogen, results only in oxidation of the hydrazine. Other types of alkylating agents, such as epoxides and α,β -unsaturated carbonyl compounds, etc., have occasionally been used with success.

Monoaryl hydrazines can be prepared quite successfully by direct arylation of hydrazine with aryl halides activated toward nucleophilic

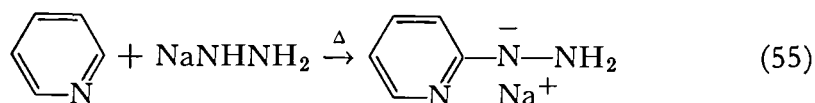
attack, such as 2,4-dinitrochlorobenzene or α -chloropyridine,⁷⁰ and this is, in fact, the best way of preparing the carbonyl reagent, 2,4-dinitrophenylhydrazine.⁷¹ In the absence of a suitably activated halogen, an activated nitro group may be displaced (as NO_2^-) by the hydrazino group,⁷² in accord with the general principles of nucleophilic attack on benzene derivatives. Displacement of halide cannot usually be forced when nitro groups are present, however, for the side reactions of reduction of nitro groups and cyclization to benzotriazole N-oxides may become dominant.⁷³ Arylation with phenols is applicable in the naphthalene series by use of the Bucherer reaction conditions⁷⁴ (NaHSO_3 catalyst) (Eq. 53), but phenol itself gives only a poor yield of phenylhydrazine.



Alkylation of hydrazine beyond the monoalkyl stage can be blocked by using an azine; benzaldazine is the usual one. The blocking groups are easily removed by hydrolysis. This method works very well for making methylhydrazine⁷⁵ (Eq. 54), but unfortunately, azines are poor nucleophiles, and only fairly reactive alkylating agents will alkylate them.



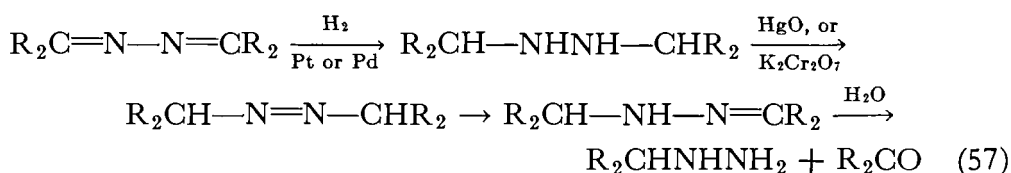
Pyridyl, quinolyl, and isoquinolyl hydrazines have been prepared from the corresponding parent substances by heating with sodium hydrazide,⁶ NaNHNH_2 (Eq. 55). This is, of course, a variant of the well-known Tschitschibabin reaction of sodamide on pyridine and analogs. Reported yields vary from 25–76%.



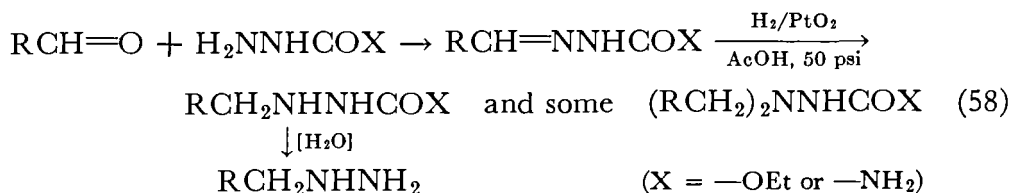
Many reductive methods are known for preparing monoalkyl hydrazines. The most general for primary alkyl groups appears to be the lithium aluminum hydride reduction of hydrazides⁷⁶ (Eq. 56). Reduction of aldazines, or the more difficultly prepared aldehyde hydrazones,



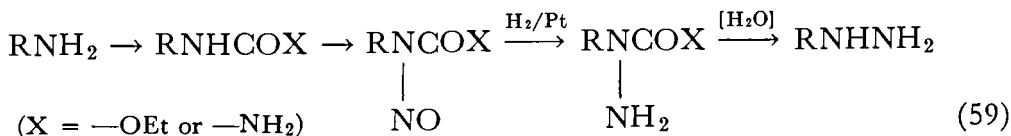
also gives primary alkyl hydrazines; sodium amalgam or hydrogen and platinum or palladium are the usual reagents.^{77, 78} With azines, of course, the amount of reduction must be controlled so that only one of the C—N double bonds is reduced; the resulting hydrazone must then be hydrolyzed. Reduction of ketazines gives secondary alkyl hydrazines; sodium amalgam does not reduce ketazines, however, and catalytic hydrogenation must be used. Some chemists have preferred to allow the reduction to go all the way to *sym*-disubstituted hydrazines and then to oxidize these to azo compounds, which are readily isomerized to the hydrazone that would have been produced by partial reduction^{77, 79} (Eq. 57). A modification of the reduction of hydrazones is reductive alkylation of hydrazine⁸⁰ by treating a mixture of ketone and hydrazine hydrochloride with hydrogen and a platinum catalyst.



Reduction of semicarbazones,⁸¹ $\text{R}_2\text{C}=\text{NNHCONH}_2$, or carboethoxy hydrazones,^{82, 83} $\text{R}_2\text{C}=\text{NNHCOOEt}$, by catalytic hydrogenation gives good yields of the corresponding alkyl hydrazides, which are easily hydrolyzed to hydrazines (Eq. 58). There is considerable advantage in utilizing this route, for all of the original ketone or aldehyde moiety is converted to hydrazine (rather than half as in the case of azines), and these substituted hydrazones are much easier to prepare and handle than are unsubstituted hydrazones (see the following section).

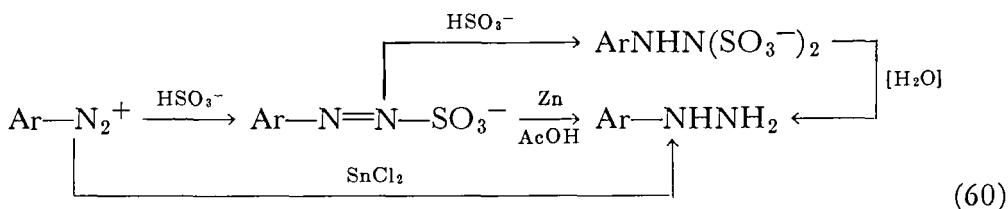


Nitroso ureas and nitroso urethans also give hydrazides on catalytic hydrogenation; hydrolysis of the products gives hydrazines^{84, 85} (Eq. 59). Since the nitroso compounds are prepared from alkyl ureas or urethans, which are in turn easily prepared from amines, this route constitutes a synthesis of hydrazines from amines.

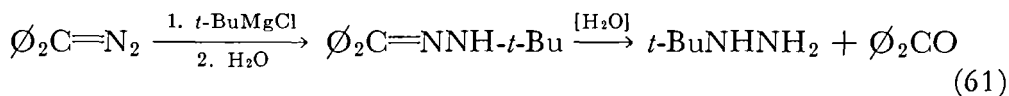


Although aliphatic diazo compounds can be reduced to hydrazines, the process is not regarded as a useful synthesis for alkyl hydrazines.

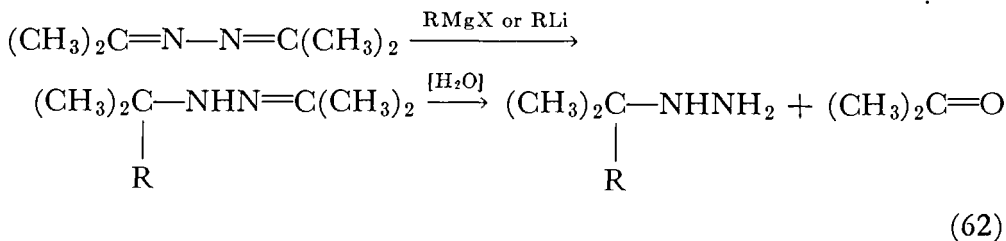
The intermediates required to prepare most diazo compounds can be converted directly to a hydrazine more efficiently. The reduction of aromatic diazonium salts, however, is the major source of aryl hydrazines.⁸⁶⁻⁸⁸ Reduction must be carried out by dissolving metals or stannous chloride. Since diazonium salts usually have low stability and cannot be heated to speed up an otherwise slow reduction, it may be necessary to make use of Fischer's device of converting the diazonium salt to a more stable arylazosulfonate salt by reaction with sodium bisulfite; reduction can then be carried out vigorously (Eq. 60). The stannous chloride method, however, has been recommended as generally better.⁸⁶



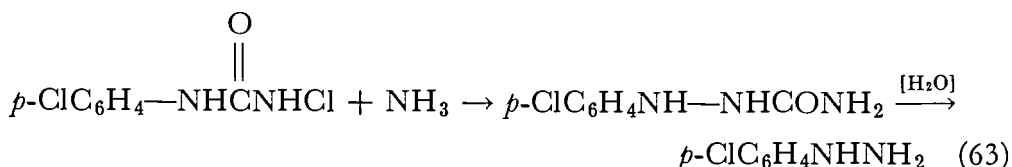
Aliphatic diazo compounds can be used as sources of hydrazines in an entirely different way, discovered by Zerner in 1913. Grignard reagents are added to the diazo group, forming hydrazones, which can then be hydrolyzed to give the hydrazine corresponding to the Grignard reagent^{89, 90} (Eq. 61). Excess Grignard reagent may cause reduction or further addition, so the method is not always successful, but it appears to be the best method to prepare *tert*-butylhydrazine. A related synthetic method is the addition of Grignard reagents to diazirines (see page 143).



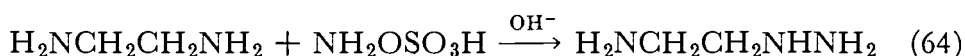
Organometallic reagents can also be used in another way for the preparation of hydrazines. They can often be induced to add to the $\text{C}=\text{N}-$ group of azines much as they do to carbonyl groups. If only one mole of organometallic reagent is used, the product is a monosubstituted hydrazone,⁹¹ from which the hydrazine can be obtained by hydrolysis (Eq. 62). The most serious limitation of the method seems to be the incursion of a competing acid-base reaction when the azine has α -hydrogens, destroying the Grignard reagent.



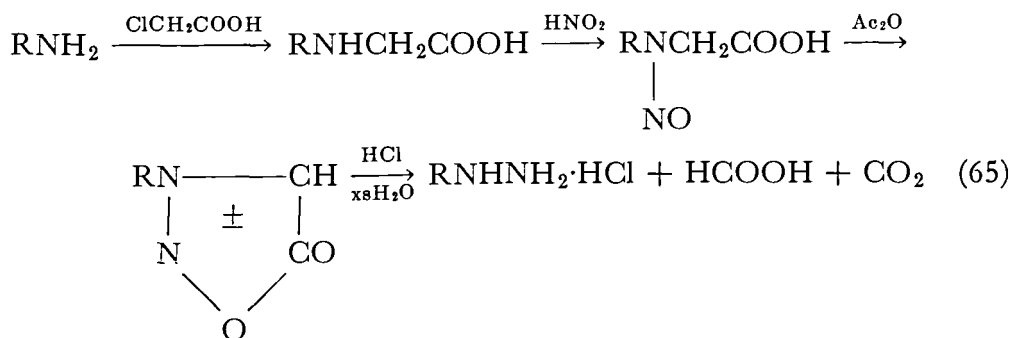
There are three additional methods that accomplish the overall conversion of amines to hydrazines; none appear to be widely used, although they are potentially quite useful. One is due to Shestakov, who showed that urea can be converted to hydrazine by treatment with hypochlorite and base.⁹² The reaction is formally analogous to the Hofmann rearrangement of N-halo amides, but, contrary to the original claims, is not generalizable to alkyl ureas,⁹³ although aryl hydrazines have been obtained from aryl ureas in this way^{94, 95} (Eq. 63). A reaction that may



be related is the amination of amines with chloramine or hydroxylamine-O-sulfonic acid, effectively the Raschig synthesis of hydrazine carried out with an amine in place of ammonia (Eq. 64). It appears to be a nucleophilic displacement by the amine on the nitrogen of the aminating agent.⁹⁶⁻⁹⁹ Yields are moderate.

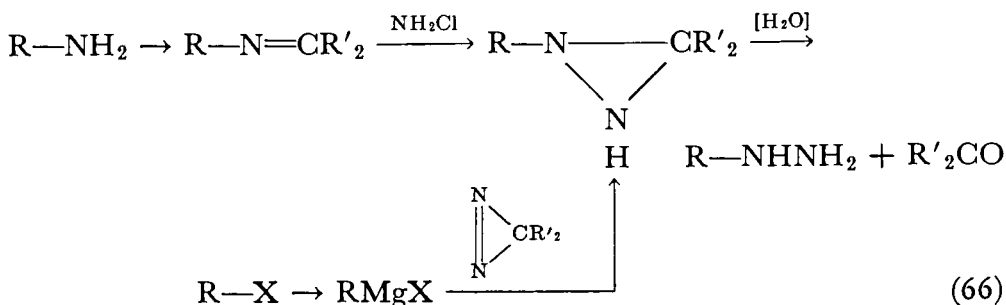


The hydrolysis of sydnones is the heart of the other method of converting primary amines to monoalkyl hydrazines. The required sydnones are mesoionic oxadiazole derivatives and are prepared from a primary amine and chloroacetic acid in three steps, generally in good yield ^{100–102} (Eq. 65).

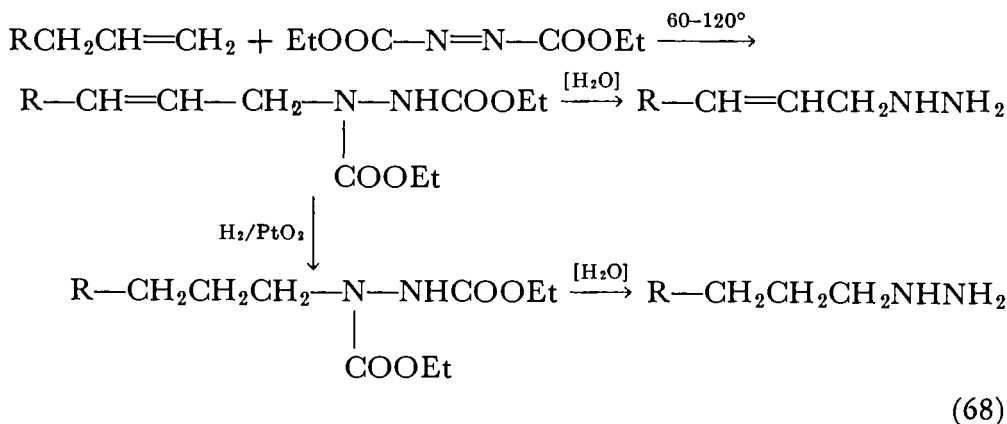
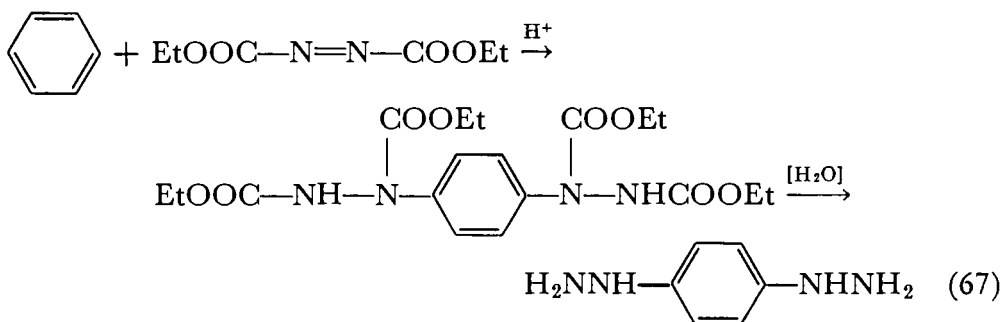


A method of potential value for the preparation of monosubstituted hydrazines is the hydrolytic cleavage of diaziridines (Eq. 66), although it has not yet been used widely for preparative purposes.¹⁰⁸ The required diaziridines are obtainable either by the reaction of chloramine with ketimines, or by the addition of Grignard reagents to diazirines; the ultimate starting materials are thus primary amines or alkyl or aryl halides. These reactions have been made the basis for an industrial

process for large-scale production of unsubstituted hydrazine, using unsubstituted ketimines and chloramine.

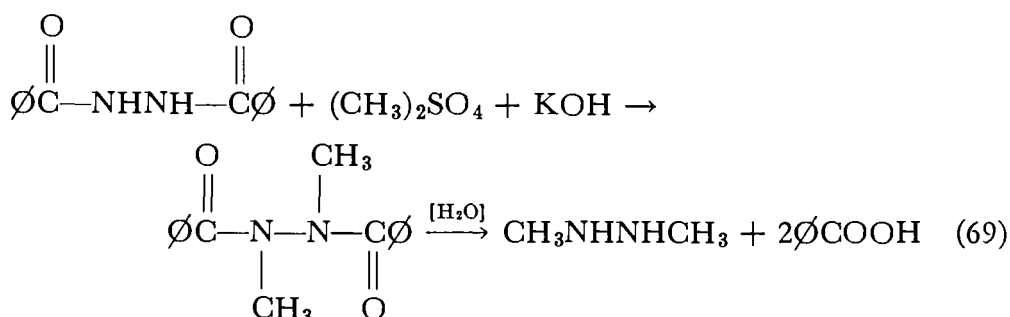


Oléfins and aromatic hydrocarbons can be converted to hydrazines through reaction with azodicarboxylic ester.¹⁰⁴ The primary products are hydrazides (N,N'-dicarboethoxy hydrazines), which are easily hydrolyzed (Eqs. 67, 68). This method has the advantage that primary alkyl hydrazines can be prepared without the danger of getting di- and polyalkyl compounds.

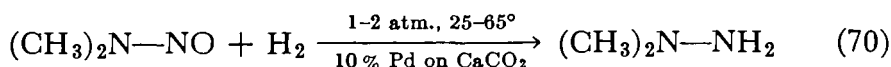


DISUBSTITUTED Direct alkylation is not usually a useful process for the synthesis of *sym*- or *unsym*-disubstituted hydrazines, since on the one hand it is difficult to stop at the dialkyl stage and on the other hand may

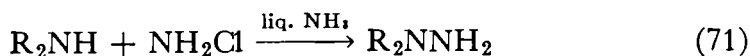
give mixtures of *sym* and *unsym* isomers.² With bulky alkylating agents, however, such as triphenylmethyl, both of these objections are reduced or disappear, and *sym*-disubstituted hydrazines may be obtained in useful yields. The usual device is to block further alkylation by using a secondary hydrazide, such as *sym*-diformyl or *sym*-dibenzoyl hydrazide. Such compounds can be alkylated once on each nitrogen by most unhindered alkylating agents, giving dialkyl hydrazides that can be easily hydrolyzed to *sym*-dialkyl hydrazines by boiling with aqueous mineral acid¹⁰⁶ (Eq. 69).



For *unsym*-disubstituted hydrazines, the almost invariably chosen route is reduction of the nitrosamine prepared from a secondary amine. The nitrosamines are easily prepared from dialkyl, alkyl aryl, and diaryl amines, and the reduction proceeds smoothly with lithium aluminum hydride, hydrogenation over a palladium catalyst, zinc and acetic acid, or with sodium and alcohol, among others¹⁰⁶⁻¹¹⁰ (Eq. 70) (see Chapter 15). *Unsym*-dialkyl hydrazines have also been prepared by direct



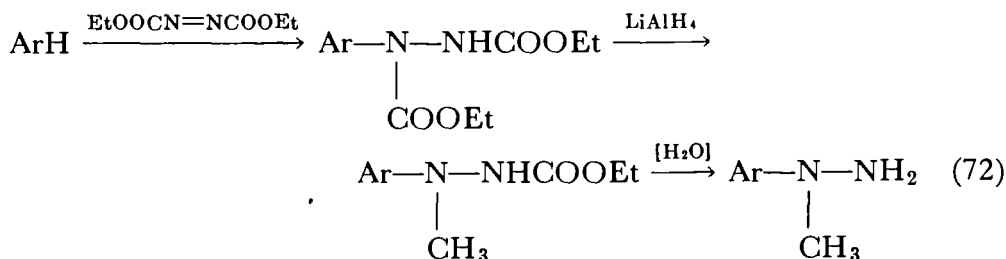
amination⁹⁶⁻⁹⁹ of secondary amines with hydroxylamine-O-sulfonic acid, chloramine, or O-mesitylhydroxylamine¹¹¹ (Eq. 71). *Unsym*-aryl alkyl



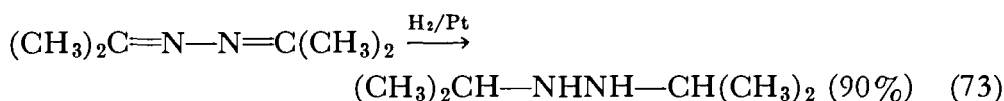
hydrazines can in some cases be prepared by arylation of an alkyl hydrazine with a highly activated aryl halide^{28, 29} (see the preceding section on reactions).

N-Methyl arylhydrazines are available from the partial reduction of the N,N'-dicarboethoxy arylhydrazines obtained from the reaction of azodicarboxylic ester with aromatic hydrocarbons; the ester group on

the substituted nitrogen is preferentially attacked by lithium aluminum hydride ¹¹² (Eq. 72).



Sym-disubstituted hydrazines can be made in wide variety by complete reduction of azines.^{79, 113} Sodium amalgam is useful for the purpose, but does not work well with purely aliphatic ketazines. Hydrogenation over platinum in the presence of acid is a more general method (Eq. 73), and lithium aluminum hydride has also been used with success.^{30b, 79} Reduction of *N'*-substituted hydrazides also gives *sym*-disubstituted hydrazines ¹¹⁴ (Eq. 74) and is especially useful when two different substituents

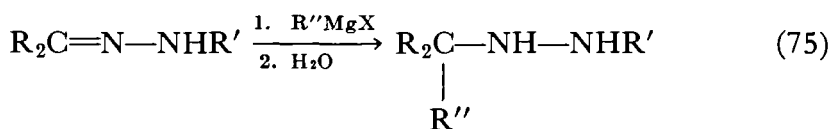


are required. This method works equally well with *N*-substituted hydrazides to produce *unsym*-disubstituted hydrazines.

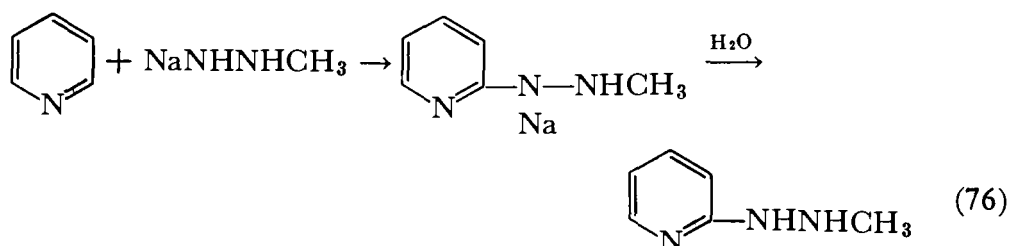


zides to produce *unsym*-disubstituted hydrazines.

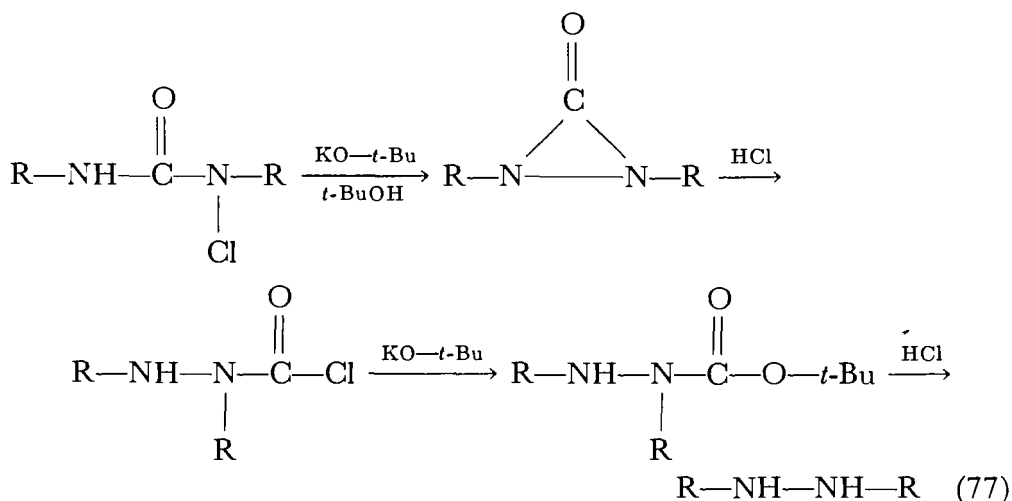
TRISUBSTITUTED Monoalkyl hydrazones can in some cases be induced to add organometallic reagents to give *sym*-dialkyl hydrazines ^{91, 115–117} (Eq. 75). The advantage of this reaction is that it is suited to the preparation of hydrazines with two different groups, and when ketone hydrazones are used, a tertiary alkyl substituent results.



A reaction of obviously limited application is the Tschitschibabin method utilizing sodium alkylhydrazides, NaNHNHR . These substances react with pyridine and its analogs to replace an α hydrogen with the β -alkylhydrazino group,⁶ $\text{RNHNH}-$ (Eq. 76).



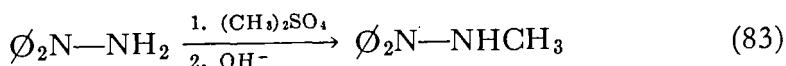
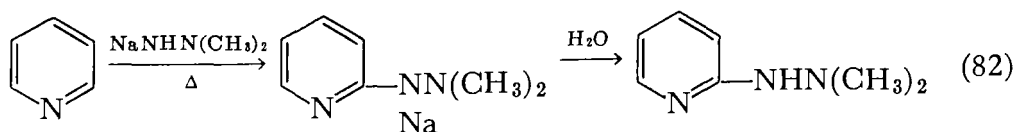
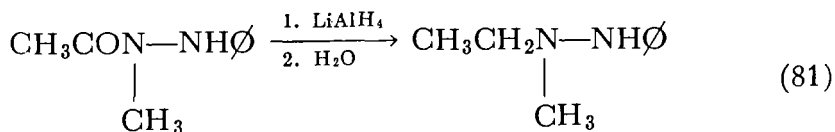
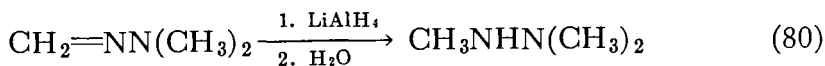
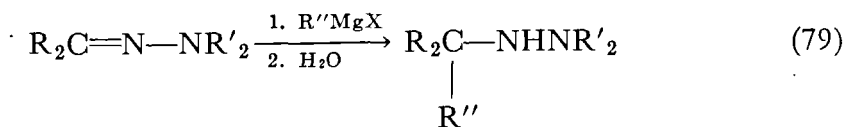
A newer preparative method that is particularly good for *sym*-di-*tert*-alkyl hydrazines starts with primary amines, from which the N-chloro derivative of a symmetrical urea can be prepared in two steps. Potassium *tert*-butoxide converts such compounds to diaziridinones, which can be readily cleaved to hydrazines ¹¹⁷ (Eq. 77).



Sym-diaryl hydrazines, commonly called hydrazobenzenes, are available in wide variety through reduction of aromatic nitro compounds by various means under neutral or alkaline conditions ²⁶ (Eq. 78) (see Chapter 14).



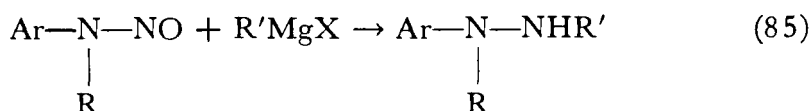
Trisubstituted hydrazines can be prepared by several of the reactions described for less substituted compounds, notably addition of organo-metallic compounds to hydrazones, reduction of hydrazones,¹¹⁸ reduction of hydrazides,^{114, 119} the Tschitschibabin reaction with sodium dialkylhydrazides, and in certain cases, direct alkylation (Eqs. 79–83).



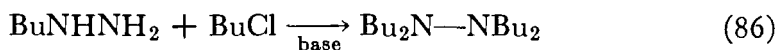
In addition to the above methods, the addition of organometallic reagents to azobenzenes (Eq. 84) has possibilities,¹²⁰ although yields are low owing to concurrent oxidation-reduction. Another route utilizing organometallic reagents is the reaction of Grignard reagents with nitros-



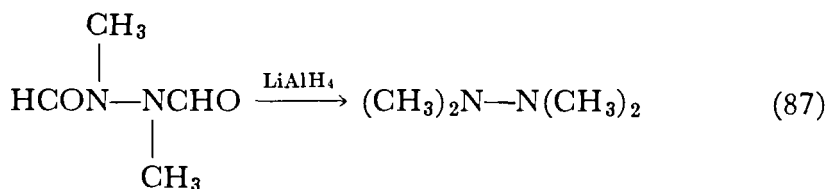
amines¹²¹ (Eq. 85). A hydroxyhydrazine is presumably formed first (as its magnesium salt), but more Grignard reagent reduces it to a hydrazine.



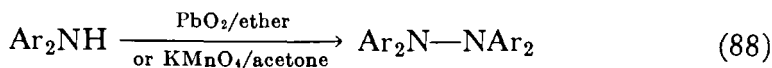
TETRASUBSTITUTED Tetrasubstituted hydrazines have been prepared in many instances by direct alkylation (Eq. 86), starting with hydrazine or its mono-, di-, or trisubstituted derivatives.^{2, 14} The major limitations are that small, reactive alkylating agents, such as methyl iodide, favor alkylation at only one nitrogen, to produce quaternary hydrazinium salts, whereas alkylating agents with secondary groups, even isopropyl,



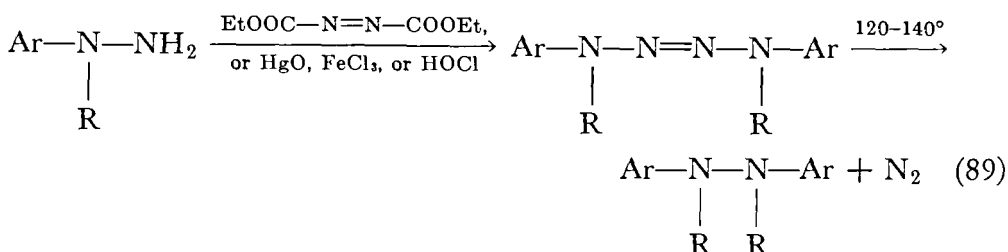
are usually incapable of adding a fourth alkyl group. Many tetrasubstituted hydrazines are prepared conveniently by reduction of *sym*-dialkyl diacyl hydrazines, a method particularly suitable for tetramethylhydrazine (Eq. 87).



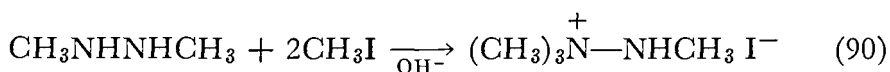
Neither of the foregoing methods is adaptable to the preparation of tetraaryl hydrazines. These are instead prepared by oxidation of diaryl amines (Eq. 88) with lead dioxide or potassium permanganate.¹²² An



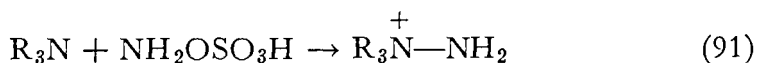
alternative oxidative method is the conversion of *unsym*-disubstituted hydrazines to tetrazenes, which decompose to tetrasubstituted hydrazines and nitrogen on heating ¹²³ (Eq. 89).



Quaternary hydrazinium salts are generally formed by direct alkylation of less substituted hydrazines (Eq. 90), as long as the groups involved are not too large.⁵ Methylation is nearly always successful in producing quaternary salts, but with larger groups alkylation usually stops short of quaternization. Tetrasubstituted hydrazines have not yet been successfully converted to quaternary salts.



Quaternary hydrazinium salts can also be obtained by the hydrolysis of quaternary hydrazonium salts ^{124a} ($\text{R}_3\text{N}^+-\text{N}=\text{CR}_2 \text{X}^-$) and quaternized hydrazides ($\text{RCONH}-\text{NR}_3^+ \text{X}^-$), and by amination of tertiary amines with chloramine or hydroxylamine-O-sulfonic acid ^{5, 124b} (Eq. 91).



HYDRAZONES

NOMENCLATURE

For all ordinary purposes, hydrazones are named as derivatives of the corresponding aldehyde or ketone by adding the separate word "hydrazone," with prefixes for any substituents on the nitrogen, as in benzophenone hydrazone, $\text{C}_6\text{H}_5\text{C}=\text{NNH}_2$, and pentanone-3 acetylmethylhydrazone, $\text{Et}_2\text{C}=\text{N}-\text{N}(\text{CH}_3)\text{COCH}_3$. They are listed under the parent ketone or aldehyde in *Chemical Abstracts*. In the exceptional case where

it may become necessary to name hydrazones as substituted hydrazines, the ketone or aldehyde moiety can be expressed in a prefix with the ending -ylidene, as in *p*-(isopropylidenehydrazino)-benzenesulfonic acid, $p\text{-(CH}_3)_2\text{C=N-NH-C}_6\text{H}_4\text{SO}_3\text{H}$. Carbamylhydrazones are a special case and are by custom invariably called semicarbazones. *Bis*-hydrazones of α -diketones are commonly called osazones.

The hydrazones formed by reaction of hydrazine with two moles of carbonyl compound, one at each end, are known as azines (or aldazines and ketazines). They are named either by following the name of the carbonyl compound with the word azine, as in "acetone azine," $(\text{CH}_3)_2\text{C=N-N=C(CH}_3)_2$, or by use of -aldazine and ketazine as suffixes, as in benzaldazine, $\text{C}_6\text{H}_5\text{CH=N-N=CHC}_6\text{H}_5$, and diethyl ketazine, $\text{Et}_2\text{C=N-N=CEt}_2$.

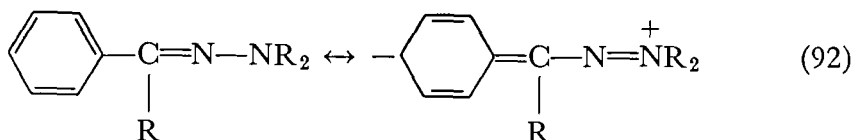
PROPERTIES

The simple alkyl-substituted hydrazones are mostly liquids, soluble in water if the carbon content is small. Formaldehyde dimethylhydrazone, for example, melts at -103° and boils at 72° at 730 mm. Phenylhydrazones are usually solids, but many of the aliphatic ones have quite low melting points, a phenomenon that has led chemists to adopt the higher melting *p*-nitrophenylhydrazones and 2,4-dinitrophenylhydrazones as derivatives for the identification of aldehydes and ketones. Azines are mostly solids.

Hydrazone formation lowers the basicity of the nitrogen atom taking part in double-bond formation, in the same way that imine formation lowers the base strength of amines (see Chapter 7). Thus hydrazones derived from hydrazines in which the reactive —NH_2 group obviously has the more basic nitrogen, such as phenylhydrazones and semicarbazones, are noticeably weaker bases; semicarbazones are about 5 powers of 10 weaker than semicarbazide.¹²⁵ Azines, in which both nitrogens are bound by double bonds, are usually insoluble in dilute acids; acetone azine, however, is reported^{126a} to have $\text{pK}_b = 9$. Unsubstituted and alkyl-substituted hydrazones of aryl ketones are of special interest, because of the possibility of pi-electron delocalization spanning the C=N double bond. Benzophenone hydrazone, $\text{pK}_a = 3.85$ (measured in anhydrous methanol,^{126b}) is a very much weaker base than hydrazine itself ($\text{pK}_a = 8.07$). The outer nitrogen of hydrazones evidently interacts appreciably with the substituents on the carbon, for *p,p'*-dimethoxybenzophenone hydrazone, $\text{pK}_a = 4.70$, is stronger than the parent compound, and *p,p'*-dichlorobenzophenone hydrazone, $\text{pK}_a = 3.13$, is significantly weaker. These substances thus behave as vinyls of aniline. The electronic

interaction between the amino group and the C-phenyl group is best described in terms of a limiting structure that represents the group $R_2NN=C<$ as electron donating ^{124b, 127} (Eq. 92). Quaternary hydra-

zonium salts, $R_2C=N-NR_3^+ X^-$, appear to be derived from strong

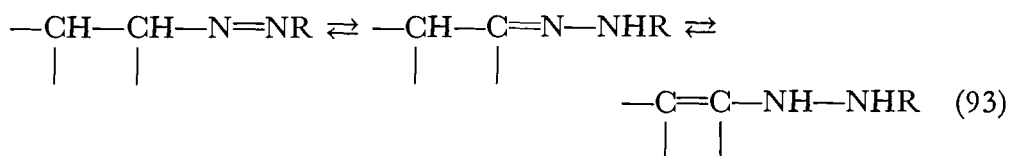


bases.^{124a}

p-Nitrophenylhydrazones and 2,4-dinitrophenylhydrazones are acidic enough to dissolve in sodium hydroxide solution. Benzaldehyde 2,4-dinitrophenylhydrazone and its simple derivatives ¹²⁸ have values of pK_a of about 11. It should be noticed, however, that hydrazone anions are

identical with those of the tautomeric azo compound: $R_2C=N-N^--R \leftrightarrow R_2C^--N=N-R$.

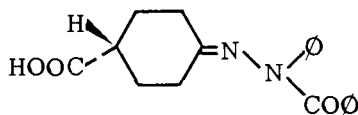
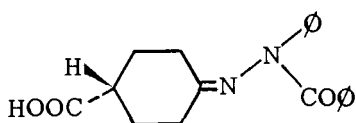
The possibility of tautomerism in hydrazones has been debated for a very long time, but it is only quite recently that physical methods became available that could distinguish between the possibilities unambiguously.¹²⁹⁻¹³¹ Monosubstituted hydrazones having at least one alpha hydrogen can in principle tautomerize to azo compounds or to vinyl hydrazines (Eq. 93), and it has often been asserted that one or another of the several forms in which hydrazones are generally encountered is an azo tautomer. Nuclear magnetic resonance evidence is convincing, however, that none of these claims is correct and that the observed forms are



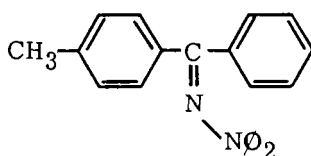
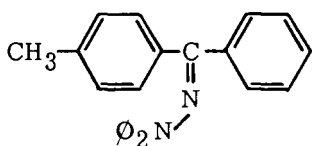
either geometric isomers, polymorphic modifications, or trimers.¹²⁹⁻¹³¹ In other cases, investigators have been misled by atmospheric oxidation of arylhydrazones of aldehydes. (Remarks on the structure of osazones appear on page 134.)

In addition, the hydrazone structure should, of course, be capable of geometric isomerism about the $C=N$ bond, a phenomenon that could only be observed with hydrazones of aldehydes or unsymmetrical ketones. Only in restricted instances was it possible to establish that different forms of hydrazones were a result of geometric isomerism before NMR.¹²⁹⁻¹³¹

An early example in which geometric isomerism was clearly demonstrated is the phenylbenzoylhydrazone of cyclohexanone-4-carboxylic acid. The geometric isomers are in this case mirror images, and in 1914, Mills and Bain ^{132, 133} succeeded in resolving it into its optical antipodes. Furthermore, the diphenylhydrazones of benzophenones, which are structurally incapable of tautomerism, have been separated into isomeric pairs in the case of the *p*-methyl- and *p*-methoxy-benzophenone derivatives.^{134a} The isomeric carboethoxyhydrazones of benzil and benzoin have also been separated.^{134b} All three possible isomers,



(optical and geometric isomerism in a hydrazone)

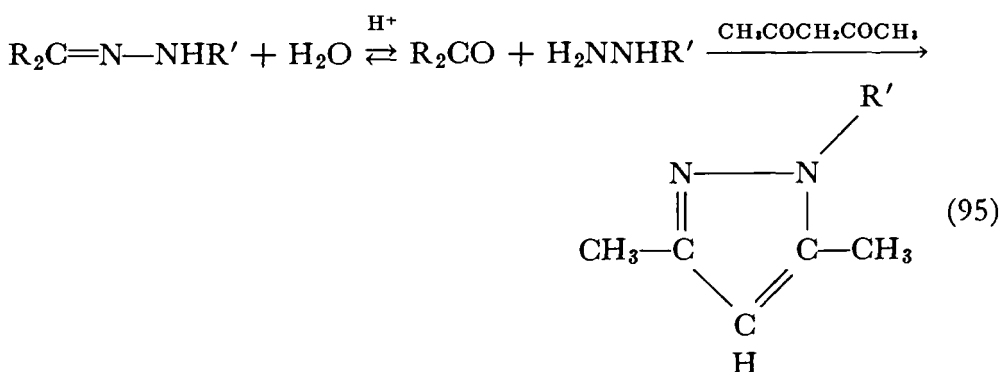


(a pair of isomeric hydrazones that has been separated)

syn-syn, *syn-anti*, and *anti-anti*, of *p*-nitroacetophenone azine have been isolated.¹³⁵

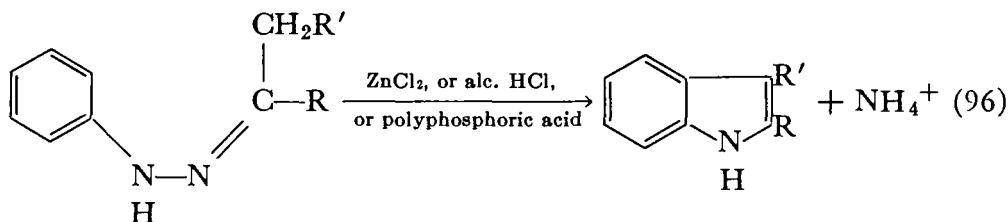
The hydrazone structure does not of itself give color to a molecule; when there is no conjugation, as in dimethylhydrazones of aliphatic ketones, there is weak absorption in the near ultraviolet ^{124a, 127, 136} at 232–234 mμ. The position of the near UV maximum for 2,4-dinitrophenylhydrazones and semicarbazones is sufficiently sensitive to structural variations in the ketone or aldehyde moiety to be a useful diagnostic tool.^{137, 138} The near-ultraviolet absorption appears much nearer the visible when the hydrazone carbon bears an aryl group; the bathochromic shift is even further pronounced when electron-withdrawing *para* substituents are present, indicating an extended delocalized electronic system.^{124a, 127, 130b} In quaternary hydrazonium salts, where the terminal

Because of the difficulty in shifting the equilibria in the direction of hydrolysis products, the use of a trap to remove the liberated hydrazine must be resorted to for efficient hydrolysis of hydrazones. Pyruvic acid is especially effective for this purpose,¹⁴¹ for it forms very stable hydrazones, but acetylacetone is also very good (Eq. 95). It acts by converting the hydrazine to the very stable pyrazole ring system. (Cleavage by nitrous acid is discussed further on). Exchange with a high-boiling ketone, such

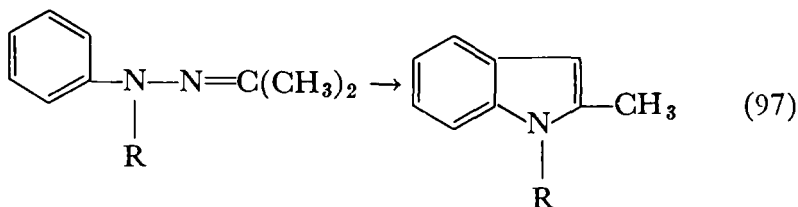


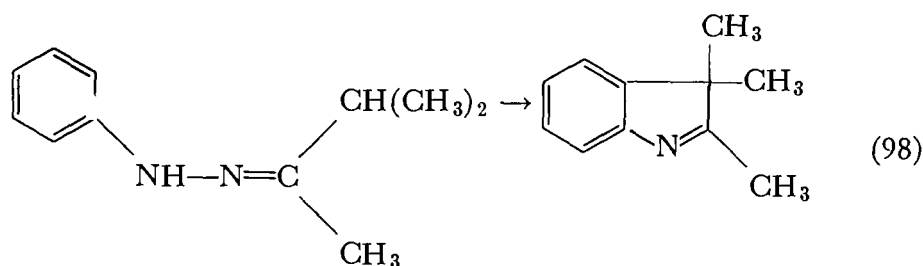
as benzophenone, with concurrent distillation of the more volatile aldehyde or ketone, has also been recommended.¹⁴²

FISCHER INDOLE SYNTHESIS Aryl hydrazones of aliphatic ketones undergo an acid-catalyzed cyclization that competes very successfully with hydrolysis; it becomes almost quantitative when anhydrous catalysts, such as zinc chloride or alcoholic hydrogen chloride, are used. Indoles and ammonia are produced (Eq. 96). The reaction is known as the Fischer indole synthesis. Since its discovery in 1886 it has become the

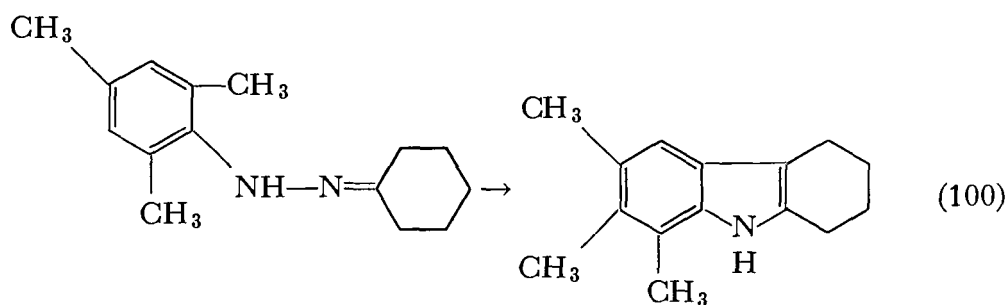
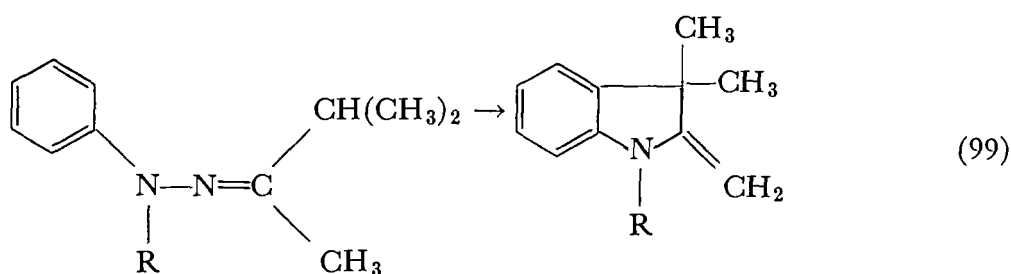


most widely used preparative method for this important heterocyclic system.¹⁴³ When there are two groups on the hydrazone nitrogen, the cyclization occurs even more easily, and N-substituted indoles are formed (Eq. 97). When the ketone moiety holds a secondary alkyl group, a true

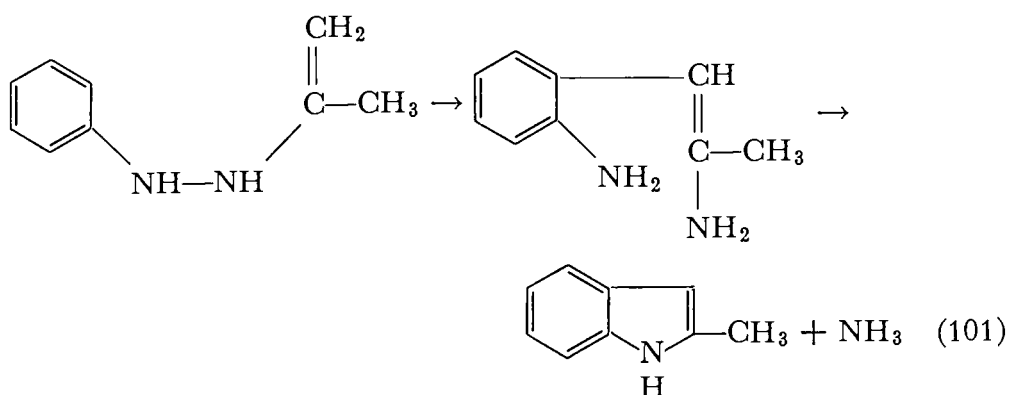




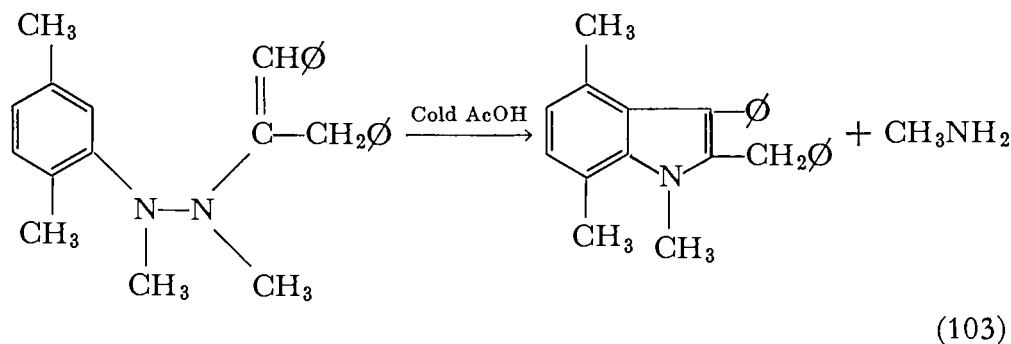
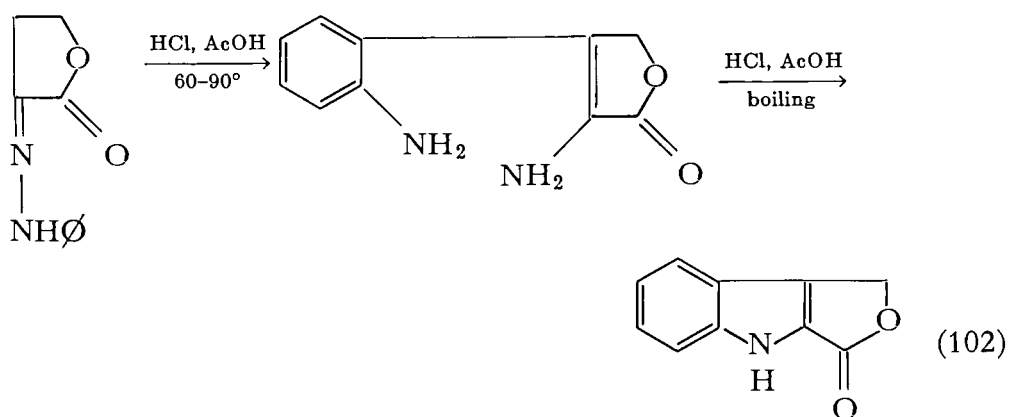
indole does not form but indolenines, which are bond-isomers of indoles, are formed instead (Eq. 98). With disubstituted hydrazones of such ketones, compounds of still another bond-isomeric structure, α -methyleneindolines, are formed (Eq. 99). Finally, when both *ortho*-positions on the phenyl group are blocked by alkylation, alkyl migration occurs so as to permit indole formation ¹⁰⁴ (Eq. 100).



The most plausible mechanism for the Fischer indole synthesis is due to Carlin,¹⁴⁴ who pointed out the similarity in form to the benzidine rearrangement. If the vinyl hydrazine tautomer of the hydrazone is first formed, a benzidine rearrangement without rotation (the so-called *ortho*-benzidine rearrangement) would give rise to an *o*-aminophenyl enamine, which would be expected to cyclize to an indole with elimination of the aliphatic amino group (Eq. 101). In one case, such an inter-

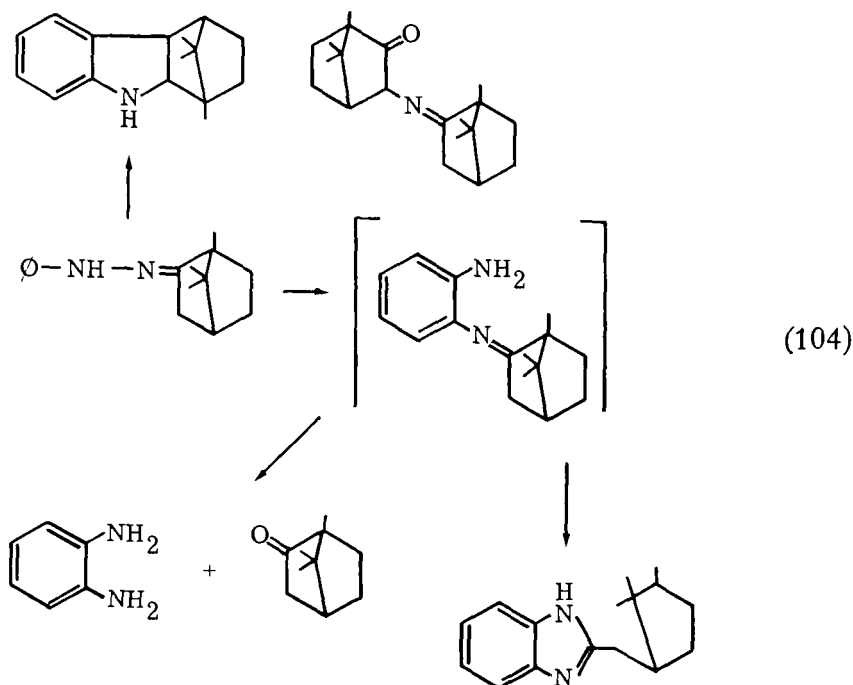


mediate diamine has actually been isolated and shown to cyclize on more drastic treatment ¹⁴⁶ (Eq. 102). Furthermore, structurally fixed vinyl hydrazines have been demonstrated to undergo conversion to an indole ¹⁴⁶ (Eq. 103). Experiments with isotopically labeled compounds have estab-

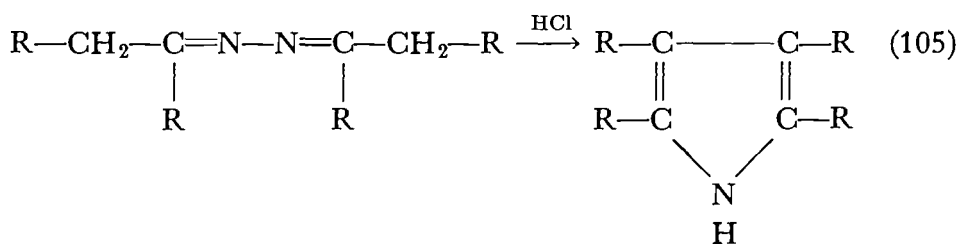


lished that it is the imine nitrogen of phenylhydrazones that is eliminated as ammonia. An unusual side reaction, observed with camphor phenylhydrazone, leads to benzimidazoles and *o*-phenylenediamine.¹⁴⁷ It has been proposed that these products originate from an intermediate

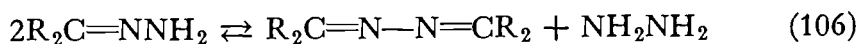
o-amino anil, formed by an intermolecular, free-radical reaction (Eq. 104) that competes with the usual one.



Azines undergo a cyclization analogous to the Fischer indole synthesis, known as the Piloty pyrrole synthesis ¹⁴⁸ (Eq. 105); it has received little attention.

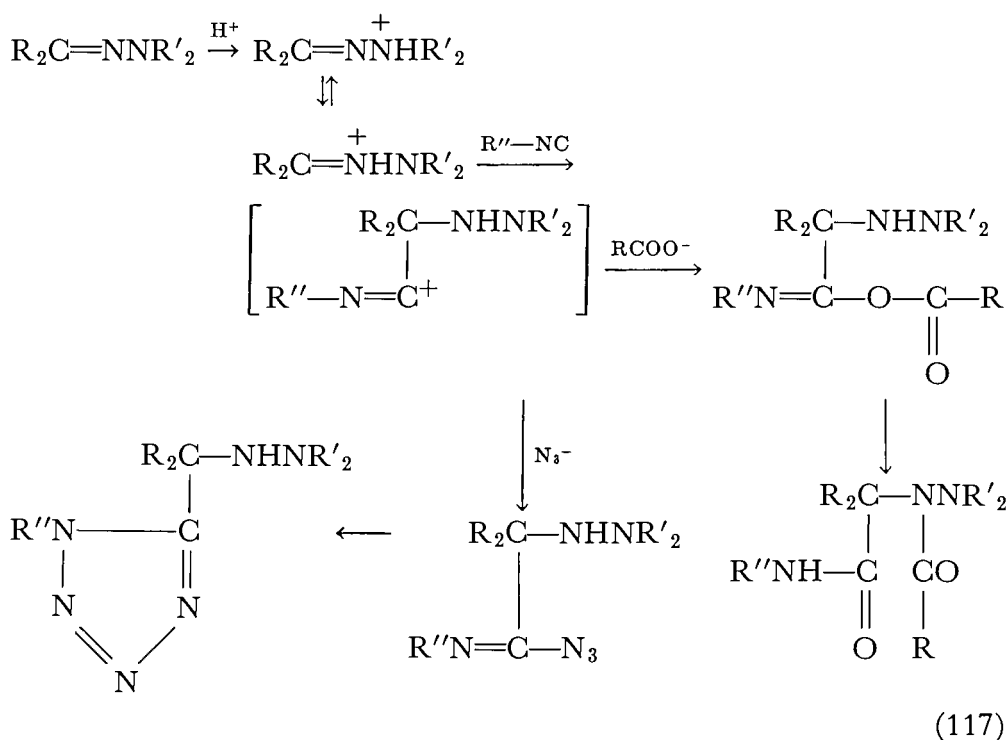
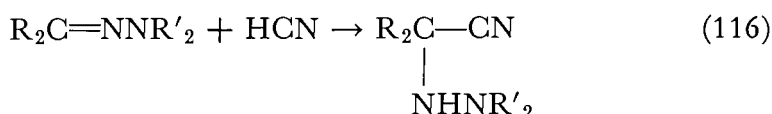


DISPROPORTIONATION Unsubstituted hydrazones undergo disproportionation to the corresponding azine and free hydrazine (Eq. 106), usually in the presence of traces of acid,¹⁴⁹ a property that makes their preparation sometimes difficult. The reaction is of course an equilibrium and so can be reversed by excess of anhydrous hydrazine. The disproportionation is the faster the more basic the hydrazone and is thus particularly easy with aliphatic hydrazones. The azines may undergo a cyclic analog of

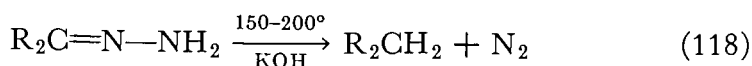


tion is believed to be between isocyanide and the conjugate acid of the hydrazone; the immediate addition product is thus a cation, which then adds the anion of the acid to give an uncharged product (Eq. 117). In many cases a further change, isomerization or cyclization, follows. Only the immonium tautomer of the two possible conjugate acids,

$R_2C=NH-NR'_2$ and $R_2C=NNHR'_2$, would be expected to have a sufficiently electrophilic carbon to condense with the isocyanide carbon, and therefore only hydrazones with base-weakening substituents on the saturated nitrogen, such as semicarbazones, take part readily in this reaction.



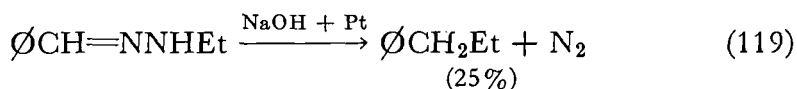
Unsubstituted hydrazones react in a useful way with strong bases, such as alkali hydroxides or alkoxides, resulting in loss of nitrogen and conversion of the alkylidene moiety to a hydrocarbon (Eq. 118). Semi-



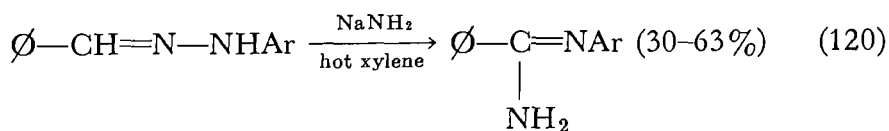
carbazones ultimately react in the same way for they are first hydrolyzed to unsubstituted hydrazones. The reaction is known as the Wolff-

Kishner reduction¹⁵⁸ and can be carried out on an aldehyde or ketone without actual isolation of the hydrazone, which may be formed *in situ*. Originally the reaction was run either with solid sodium hydroxide in the presence of platinum, or with strong alcoholic potassium hydroxide solution in sealed tubes, for the temperatures required are usually above the boiling point of the reaction medium. The introduction of ethylene glycol as a solvent by Huang Min-lon greatly increased the usefulness of the reaction by allowing it to be carried out in an open apparatus. Still a further improvement is the use of potassium *tert*-butoxide in dimethyl sulfoxide, which allows the reaction to be carried out efficiently at room temperatures.¹⁵⁹ In special cases, however, such as α -keto hydrazones, even warm, aqueous sodium hydroxide is sufficient to bring about the reaction.⁸⁸

The reaction is first order in hydrazone and first order in base, so the anion of the hydrazone is evidently formed.^{161, 162} It has been proposed that base-catalyzed tautomerization to an azo compound is a necessary and probably rate-determining step, followed either by loss of nitrogen and recombination of radicals, or by base-catalyzed loss of nitrogen to form a carbanion.^{159, 161, 162} In support of the former is the observation that N-alkyl hydrazones undergo the Wolff-Kishner reaction, giving the corresponding alkyl hydrocarbons (Eq. 119) (although in low



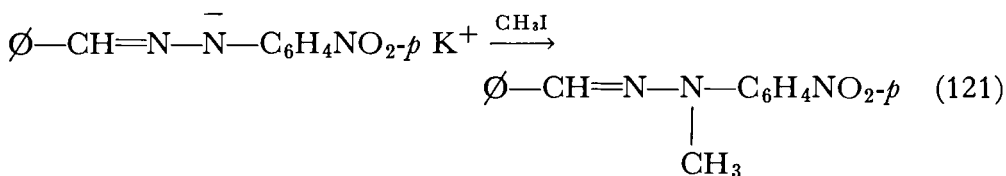
yields). Dialkyl hydrazones are quite inert, but some dinitrophenylhydrazones undergo the reaction with loss of dinitrophenol.^{161, 162} A related reaction, the base-induced cleavage of sulfonylhydrazones, is discussed in the following section on Hydrazides. Aldehyde arylhydrazones, which cannot undergo the Wolff-Kishner reaction, are susceptible to rearrangement to amidines by strong bases^{163a} (Eq. 120). It is not unreasonable to suppose that this reaction involves cleavage to a nitrile



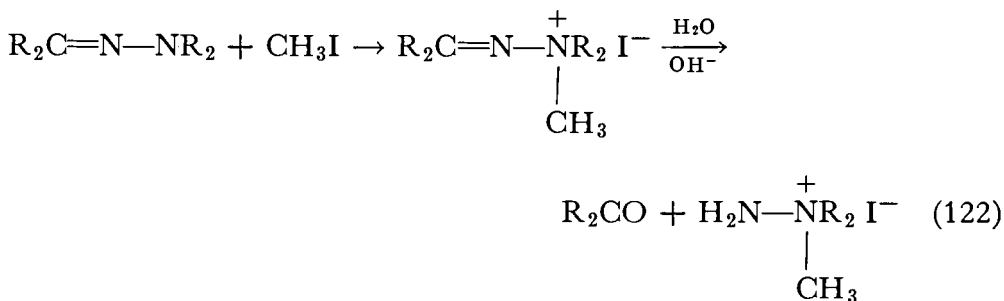
and anilide ion, followed by the known reaction of these two species to form the amidine; a route through a diaziridine seems less likely, in view of the stability of diaziridines and their magnesium derivatives prepared in other ways. Nitrile and aniline have, indeed, been obtained in addition to or instead of amidine under not very different conditions^{163b}; this

cleavage is strongly promoted by oxygen, and may involve a free-radical chain process. Some N-benzoylhydrazones are cleaved to amides by alumina or hot alkali.^{163c}

ALKYLATION Common hydrazones are apparently not readily alkylated, although there is little information on the subject. The low basicity of arylhydrazones and semicarbazones would not be conducive to alkylation, but the anions are more reactive, as shown by the benzylation of acetone acetylhydrazone in the presence of 40% sodium hydroxide and the methylation of the potassium salt of benzaldehyde *p*-nitrophenylhydrazone¹⁶⁴ (Eq. 121). Dialkyl hydrazones react readily with methyl

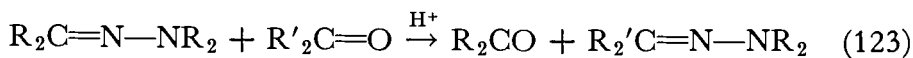


iodide, however; alkylation occurs exclusively at the singly bonded nitrogen, which must be the more strongly basic, yielding quaternary hydrazones (Eq. 122), whose structure is shown by their hydrolysis to quaternary

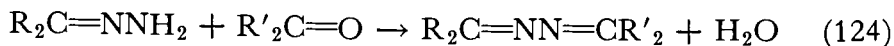


hydrazinium salts.^{129a}

CARBONYL COMPOUNDS Aldehydes and ketones can react with hydrazones in several ways. The simplest of these is perhaps acid-catalyzed

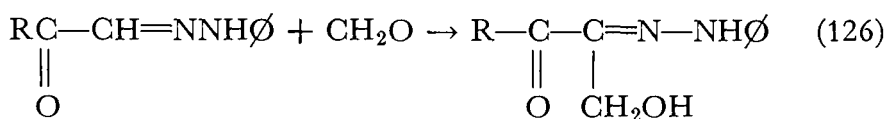
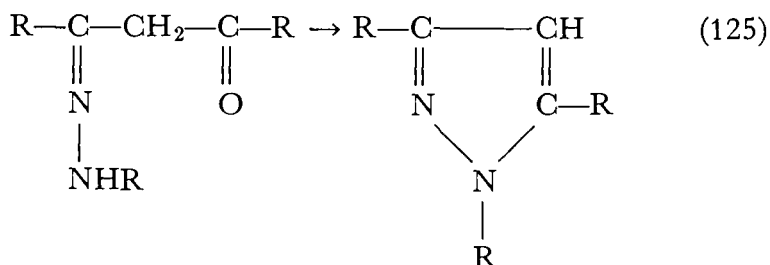


exchange (Eq. 123), which has been mentioned in connection with hydrolysis of hydrazones. Unsubstituted hydrazones react readily at the remaining amino group to give azines (Eq. 124). When a carbonyl



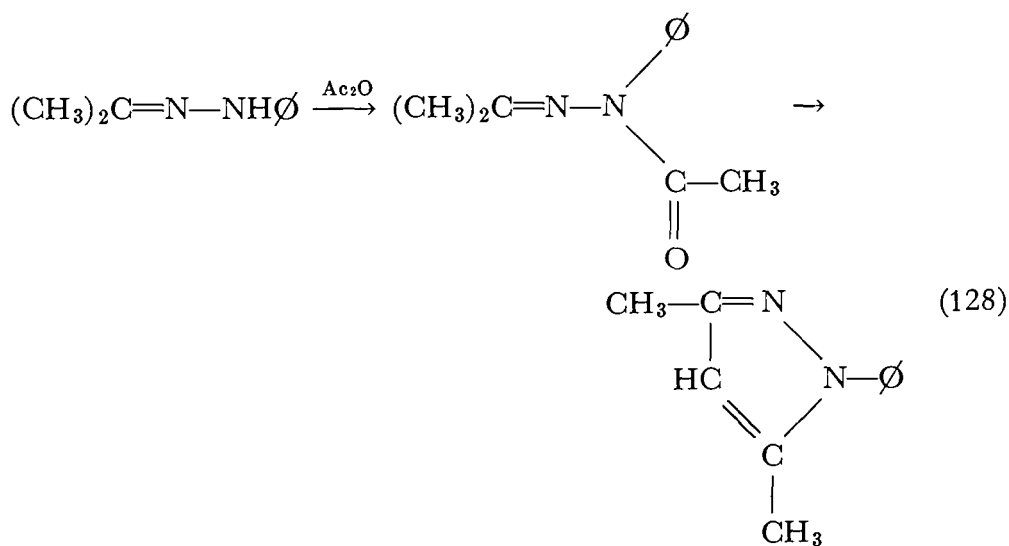
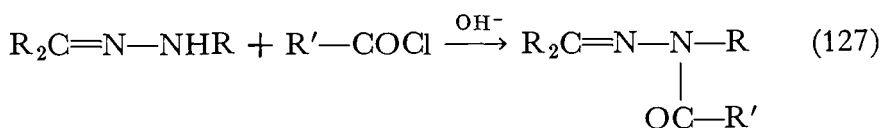
group is in a position β to the hydrazone carbon, internal reaction usually

ensues rapidly, even with monosubstituted hydrazones if enolization is possible; the products are pyrazoles (Eq. 125). A special reaction has



been reported for the hydrazones of α -keto aldehydes, which depends on the acidity of the aldehyde hydrogen. Condensation occurs rapidly with formaldehyde to produce an α -hydroxy hydrazone¹⁶⁵ (Eq. 126). It is not unlikely that the initial product is the azo tautomer.

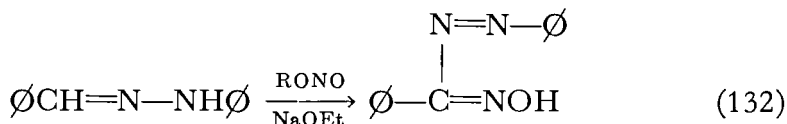
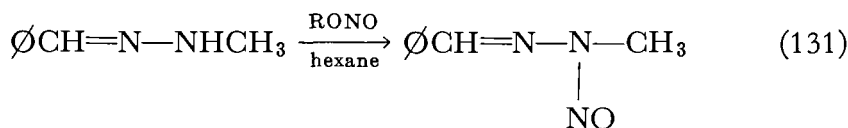
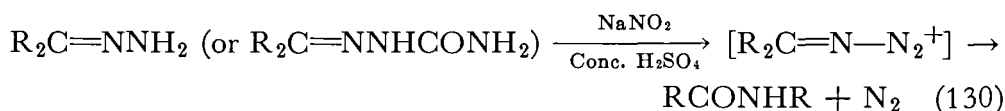
ACYLATION Acylation of hydrazones can in general be accomplished normally if there is an unsubstituted position remaining, and a number of acetyl, benzoyl, and arenesulfonyl hydrazones have been prepared from alkylhydrazones under Schotten-Baumann conditions²⁷ (Eq. 127). In some cases, however, cyclization to an active methylene group may ensue, as in the acetylation of acetone phenylhydrazone¹⁶⁶ (Eq. 128).



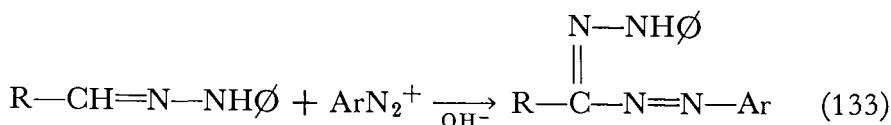
NITROSATION Nitrosation occurs differently with unsubstituted hydrazones and semicarbazones than with monosubstituted hydrazones. In the presence of water, the first two give rise either to an aldehyde or ketone (Eq. 129). So smooth is the reaction that it has been recommended as the method of choice for regenerating aldehydes and ketones



from their semicarbazones; aqueous sodium nitrite is added to a solution of the semicarbazone in glacial acetic acid. In concentrated sulfuric acid, however, a rearrangement takes place, giving amides^{168, 169} (lactams from derivatives of cyclic ketones) (Eq. 130). This is apparently a rearrangement of the Schmidt type, in which an intermediate iminodiazonium ion, also believed to be formed from ketones and hydrogen azide, is generated. Monosubstituted hydrazones are readily nitrosatable, giving reasonably stable N-nitroso hydrazones¹⁶¹; aldehyde phenylhydrazones, however, undergo C-nitrosation in the presence of base (Eqs. 131, 132) to form nitrosazones, the oxime analogs of formazans (see Chapter 11).

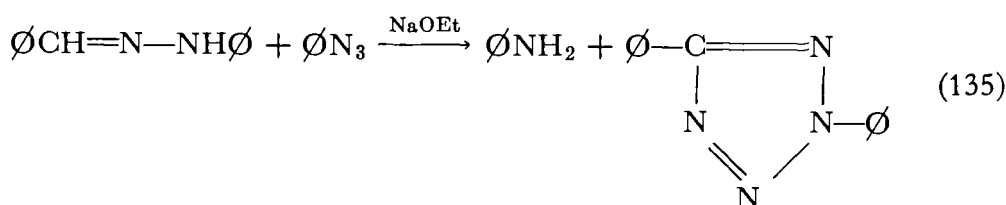
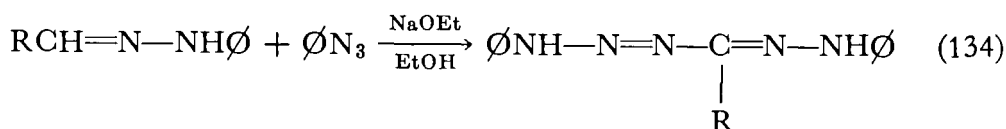


DIAZONIUM COUPLING Another case of electrophilic attack on hydrazones is the reaction of diazonium salts with aldehyde phenylhydrazones. The aldehyde carbon is the eventual site of coupling, and a class of highly colored substances known as formazans (see Chapter 11) is formed (Eq. 133). There is evidence to suggest that coupling actually takes place

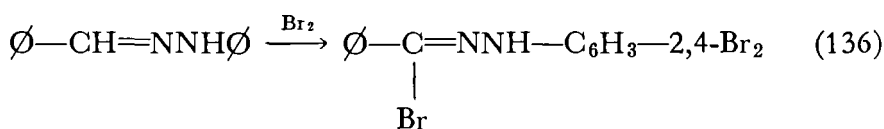


first at nitrogen, giving tetrazenes, $\text{RCH}=\text{N}-\text{N}\text{O}-\text{N}=\text{N}-\text{Ar}$, which are known to rearrange easily to formazans.¹⁷⁰ A related reaction is the

base-catalyzed coupling of aryl azides with aldehyde phenylhydrazones, which produces N-amino formazans¹⁷¹ (Eq. 134). Benzaldehyde phenylhydrazone, however, behaves differently; the N—N bond of the hydrazone is cleaved, and a 2,5-disubstituted tetrazole is produced¹⁷² (Eq. 135), possibly as a result of further reaction of the N-amino formazan.

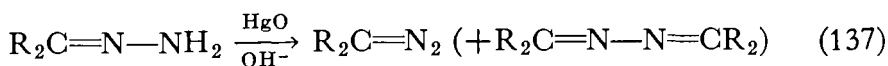


Halogenation of aldehyde hydrazones substitutes the aldehyde hydrogen, giving hydrazonoyl halides¹⁷³⁻¹⁷⁶ or their cyclization products (oxadiazoles in the case of semicarbazones), and may of course, halogenate



other parts of the molecule (Eq. 136) if they are sensitive to halogenation.

OXIDATION Oxidation of hydrazones is possible if there is no more than one substituent on nitrogen. The formation of diazoalkanes by the oxidation of unsubstituted hydrazones is an important preparative method that often gives high yields. Although many oxidizing agents have been tried, yellow mercuric oxide has kept its place as the most widely used; silver oxide, activated manganese dioxide, and mercuric trifluoroacetate also give good results.¹⁷⁷ In spite of much attention, the detailed nature of the oxidation remains uncertain. It is catalyzed by base, and a limited amount of water or alcohol is very helpful.¹⁷⁸ The yields obtained appear to depend largely on the extent to which two side reactions are promoted: decomposition of the diazo compound with loss of nitrogen, and formation of an azine (Eq. 137). The former reaction

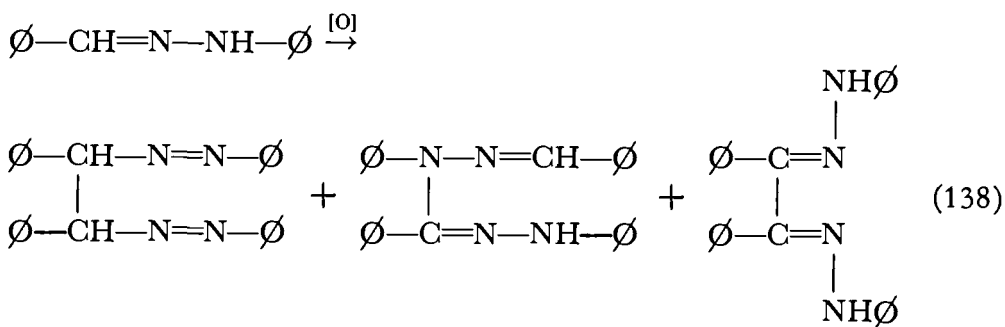


is subject to catalysis by mercury compounds, and in sensitive cases no diazo compound can be isolated at all; only its decomposition products

can be obtained.¹⁷⁹ Such a case is camphor hydrazone, whose oxidation gives tricyclene instead of diazocamphane. Azines are almost always contaminants of diazo compounds formed by oxidation of hydrazones, but they can usually be removed by virtue of their low solubility in petroleum ether. It has been proposed⁹ that they are formed by the loss of nitrogen from dimers of the diazo compounds, which might be formed by coupling between diazo compound and hydrazone followed by oxidation of the coupling product. A kinetic study of the formation of azines from diazo compounds suggests that azines are formed by the reaction of carbenes with diazoalkane, or of a diazoalkane-base adduct with another molecule of diazoalkane¹⁸⁰ (see Chapter 10).

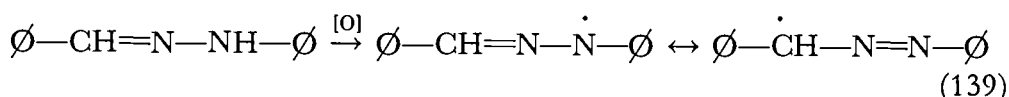
Monosubstituted hydrazones may be oxidized by a variety of reagents; the products may be dimeric, oxygen-containing, or both. Oxidation of phenylhydrazones of aldehydes, particularly benzaldehydes, by mercuric oxide, iodine, alkyl nitrites, etc., produces dimeric substances whose number and identity have for a long time been controversial.¹⁸¹⁻¹⁸⁴ Unraveling the problem was hampered by the inherent imprecision of hydrogen analyses, by the occurrence of easy further transformations, and by the existence of solid solutions. The combined evidence of nuclear magnetic resonance, infrared, and ultraviolet spectroscopy appears at last to have brought order to the area in the representative instance of benzaldehyde phenylhydrazone,^{183, 184} with which most workers have been concerned.

An initial oxidation product of benzaldehyde phenylhydrazone is a bright yellow substance, with a melting point reported variously between 180 and 186°. Although it was for a long time thought to be a tetrazane derivative, it is now firmly established as a *bis*-azo compound (Eq. 138);

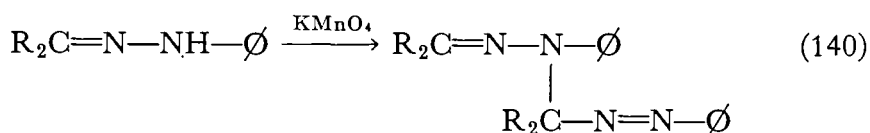


it is accompanied by an isomer, mp 203°, having a hydrazidine structure, and by *anti*-benzil osazone, mp 234°. The *bis*-azo compound is easily tautomerized by treatment with base to *anti*-benzil osazone, and all of these substances may be oxidized further. The initial step leading to them is probably the formation of a free radical (Eq. 139), which can dimerize by C—N or C—C bond formation.^{163b, 183, 184} Conditions can be

so chosen (e.g., oxygen and alcoholic alkali) so as to make the osazone the predominant product in preparatively useful yield.¹⁸¹

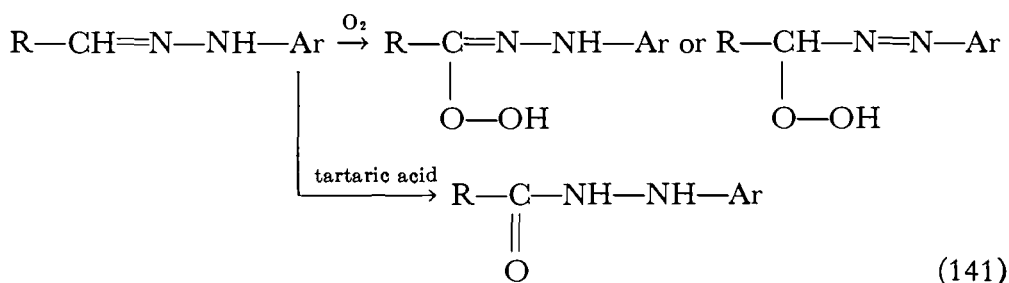


Ketone phenylhydrazones¹⁸⁵ are apparently oxidized to an analogous free radical, but dimerization takes place predominantly if not entirely by C—N bond formation (Eq. 140). The possibility for tautomerism inherent in the aldehyde hydrazone oxidation products is, of course, not

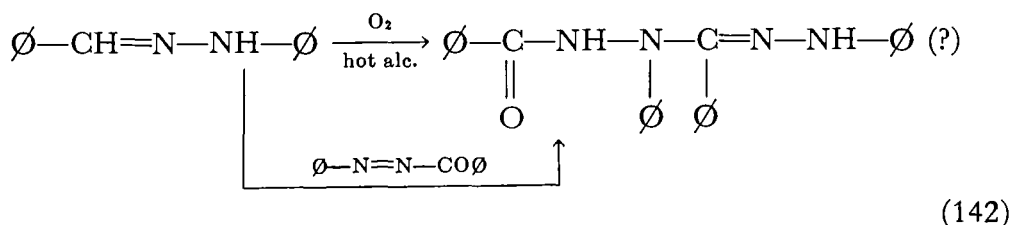


present, and the products from ketones are fixed in the azo hydrazine structure.

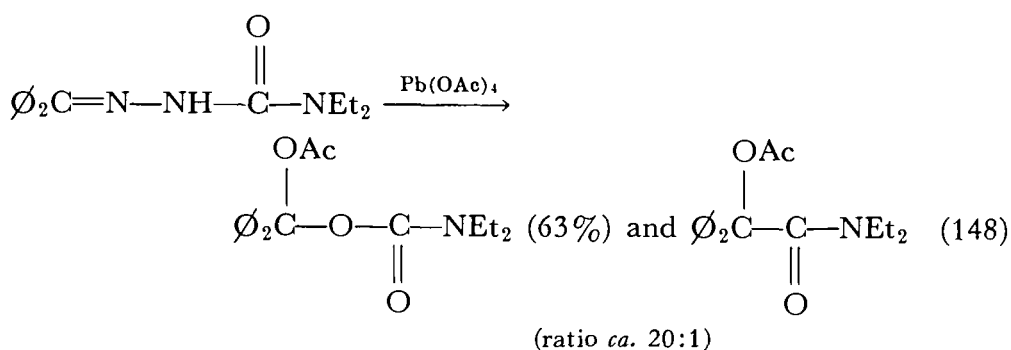
Oxidizing agents that are donors of oxygen may attack either the carbon or a nitrogen of the hydrazone structure. Arylhydrazones of aldehydes react easily with atmospheric oxygen, forming what are apparently hydroperoxides^{130b} (Eq. 141); ketone phenylhydrazones are not affected.¹⁸⁶⁻¹⁸⁸ In the presence of tartaric acid, however, benzaldehyde



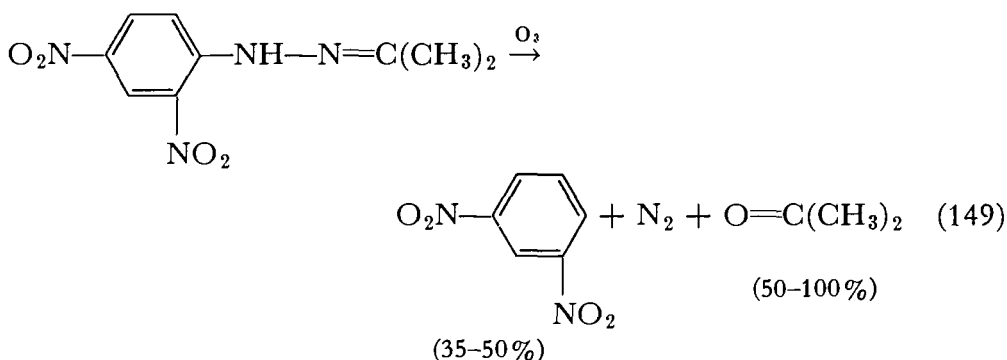
phenylhydrazone gives considerable amounts of N'-phenylbenzhydrazide, probably a transformation product of the hydroperoxide. In hot alcoholic solution, dimerization as well as oxygen addition ensues,¹⁸⁷ giving products whose structure is imperfectly established, but which appear to have an N-benzoyl hydrazidine structure (or azo tautomer) (Eq. 142).



A tetrazane structure has been proposed for such products on the basis of their known formation from the hydrazone and phenylazobenzoyl, but

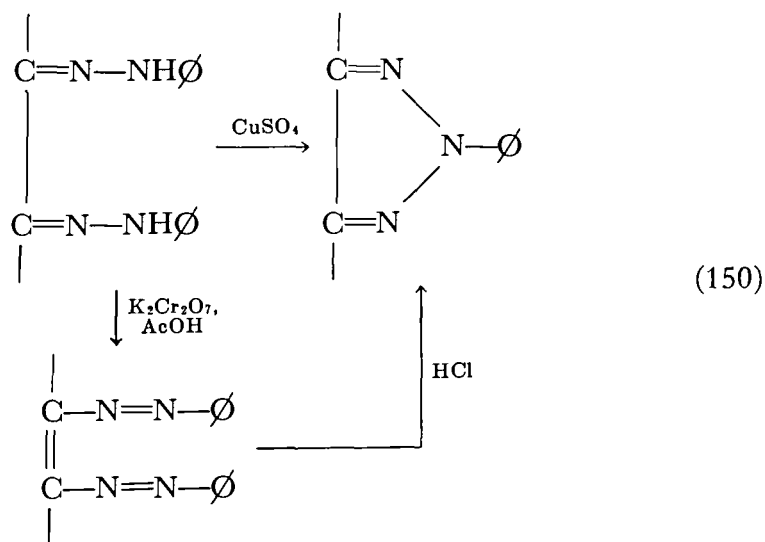


Ozone apparently attacks carbon rather than nitrogen, for ozonization of dinitrophenylhydrazones has been found to give principally ketone and dinitrobenzene (the expected product of the decomposition of



$\text{Ar}-\text{N}=\text{NH}$) ¹⁹⁴ (Eq. 149).

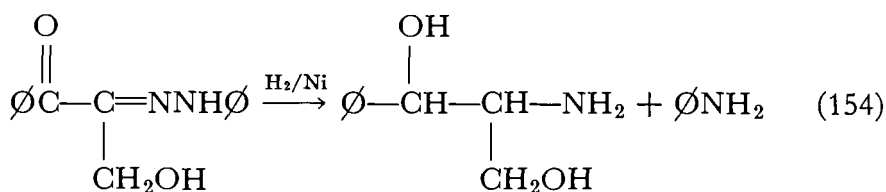
Finally, the oxidation of osazones should be mentioned. Osazones are very easily converted by copper sulfate to 2-aryl-1,2,3-triazoles, one phenyl group and its attached nitrogen being lost ¹⁹⁵ (Eq. 150). This



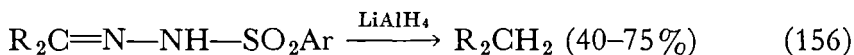
reaction is often carried out because the products, called osotriazoles, are more stable than the parent osazones, and thus make better deriva-

Sodium amalgam also reduces hydrazones to hydrazines and will reduce aromatic, but not aliphatic, azines.¹⁹⁹ Lithium aluminum hydride is an effective reducing agent for hydrazones and azines^{16, 79, 114, 200}; although it produces hydrazines, it is too powerful a reducing agent when selectivity is desired, such as when acyl groups are to be preserved. Sodium borohydride reduces disubstituted hydrazones, but gives poor results when N—H is still present.¹¹⁸

Reduction of both hydrazones and azines to amines is usually accomplished by hydrogenation with a nickel catalyst^{165, 201, 202} (Eq. 154), but zinc and alcoholic hydrogen chloride,²⁰³ as well as aluminum amalgams,^{114, 204} are also effective (Eq. 155). Reduction all the way to a methylene group has been reported of the action of lithium aluminum



hydride on tosylhydrazones²⁰⁵ (Eq. 156), and perhaps involves intermediate carbene formation.

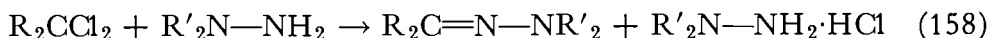
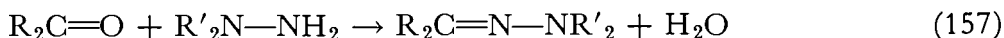


PREPARATIVE METHODS

Hydrazones are nearly always prepared from ketones or aldehydes and the appropriate hydrazine (Eq. 157), for it is a simple process that uses starting materials that are for the most part easily available. It usually suffices to mix the carbonyl compound and the hydrazine in aqueous or partly alcoholic solution, with the addition of some acid as a catalyst. For phenylhydrazones and semicarbazones, acetic acid is usually sufficient as a catalyst, but 2,4-dinitrophenylhydrazine, which is much less basic, customarily requires fairly strong solutions of sulfuric, hydrochloric, or phosphoric acid for successful hydrazone formation. Because of the great usefulness of dinitrophenylhydrazones as derivatives, many recipes have been published for their preparation,²⁰⁶ each with its own claims for advantage. Solutions of 2,4-dinitrophenylhydrazine in sulfuric acid for use in the preparation of hydrazones are sometimes called "Brady's reagent."

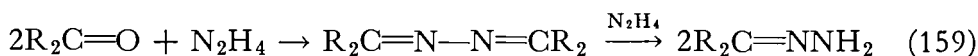
The formation of aryl and acyl hydrazones is a reaction with a very

favorable equilibrium,³⁹ for which reason it is not necessary to take pains to remove the water formed in the reaction, or even to avoid using water as a solvent. Alkyl hydrazines, on the other hand, appear to react much less completely with ketones, and the preparation of alkyl hydrazones is usually carried out at least in the absence of water and often with provision to remove the water formed in the reaction.^{136, 161} Similar remarks apply to the preparation of unsubstituted hydrazones.¹⁴⁸ The preparation of methyl hydrazones of benzaldehydes is apparently less sensitive to the presence of water, however.¹²⁷

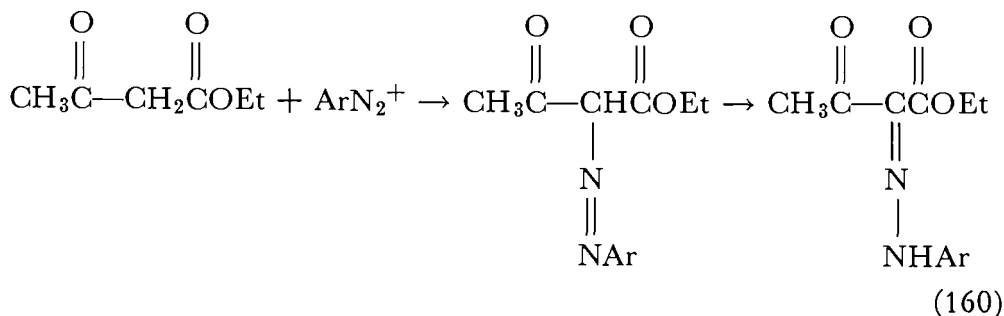


In cases where hydrazone formation from a ketone is difficult, it is sometimes advantageous to use instead the corresponding *gem*-dichloro compound²⁰⁷ (Eq. 158). Only when the ketone bears no α -hydrogens, such as in benzophenones, is it usually practical to convert a ketone to a *gem*-dichloro compound, however.

Unsubstituted hydrazones are often difficult to prepare directly, owing to the predominance of azine formation.^{126, 148} In such cases, it is sometimes convenient to prepare the azine as an initial step and then to heat the azine with excess anhydrous hydrazine to displace the equilibrium toward the hydrazone^{208, 209} (Eq. 159).



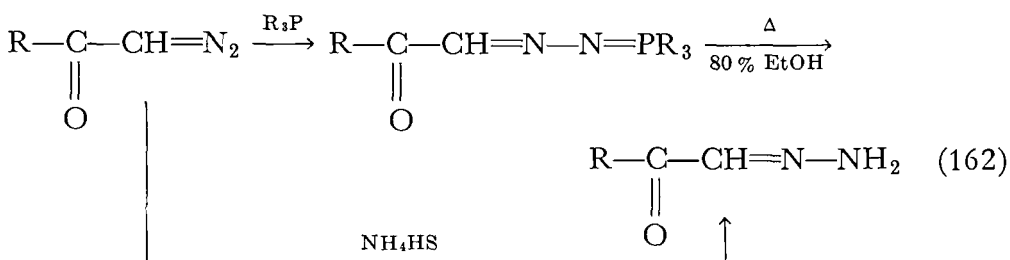
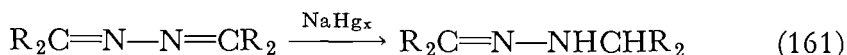
The isomerization of azo compounds to hydrazones has preparative usefulness principally in the formation of arylhydrazones from diazonium salts in the Japp-Klingemann reaction²¹⁰⁻²¹² (Eq. 160). Since this is a reaction that requires an active methylene group in the starting material, it is obviously suited for and limited to the preparation of monohydrazones of α -dicarbonyl and related compounds.



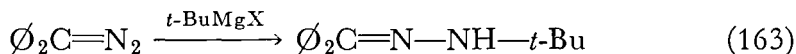
The oxidation of *sym*-dialkyl hydrazines, which gives azo compounds, can also give rise to hydrazones if conditions that favor the necessary tautomerization are chosen. The conversion of trimethylhydrazine to

formaldehyde dimethylhydrazone by oxidation with bromine has been described in the section on hydrazines (Eq. 48).

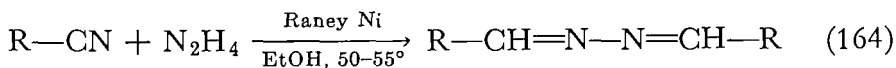
Hydrazones have been prepared reductively from azines, with the use of sodium amalgam¹⁹⁹ (Eq. 161), and from α -diazoketones with the use of either phosphines¹⁶⁰ or ammonium hydrosulfide²¹³ (Eq. 162). These reactions have the useful feature of producing monohydrazones of α -dicarbonyl compounds. The reduction of azines as a side reaction with Grignard reagents has been mentioned in the preceding section.



The addition of Grignard reagents to either azines⁹¹ (Eq. 111) or diazo compounds^{89, 90} (Eq. 163) can on occasion be managed so as to give useful yields of hydrazones.



Azines are generally prepared smoothly by treating an aldehyde or ketone with a limited amount of hydrazine; the reaction is often spontaneous, and the products, which are frequently only sparingly soluble, crystallize readily. A direct synthesis of azines from nitriles has also been reported, in which hydrazine acts as a reducing agent as well¹³⁹ (Eq. 164).



HYDRAZIDES, AMIDRAZONES, AND HYDRAZIDINES

NOMENCLATURE

Hydrazides are those compounds derived from an acid by formal replacement of a hydroxyl group by a hydrazine group, which may itself bear other substituents. Although hydrazides are known for many kinds of acids, only hydrazides of carboxylic and sulfonic acids will be given more than passing attention here.

Simple hydrazides are commonly named by replacing the -ic ending of the acid name by the suffix -(o)hydrazide, as in "acethydrazide,"

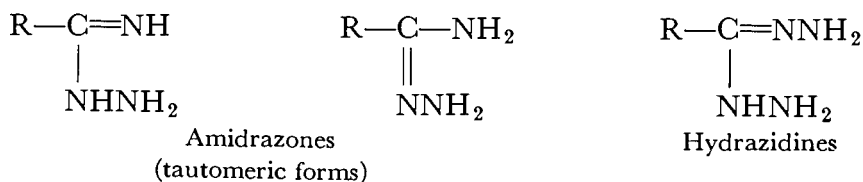
$\text{CH}_3\text{CONHNH}_2$. *Chemical Abstracts* indexes such compounds under names of the form "acetic acid, hydrazide." Less desirably, the two-word form, "acetyl hydrazide," is sometimes used. The presence of substituents on nitrogen is indicated either by the use of the locants N- and N'-, or 1- and 2-. With the latter, one must see to it that there be no ambiguity as to whether the numbers refer to the hydrazine moiety or a carbon chain. The compound $\text{C}_6\text{H}_5\text{CONHNHCH}_3$ can be called "N'-methylbenzhydrazide" or "benz-2-methylhydrazide" (or even 1-benzoyl-2-methylhydrazine).

Sym-diacyl hydrazines, RCONHNHCOR , are sometimes referred to as secondary hydrazides, with names such as "dibenzhydrazide," but when the situation is complicated by the presence of two (or more) different acyl groups, as in OCONHNHCOCH_3 , it is better to name the compounds as substituted hydrazines, as "N(or 1)-acetyl-N' (or 2)-benzoylhydrazine." Indeed, *Chemical Abstracts* indexes such compounds with inverted names, under "Hydrazine."

Hydrazides of sulfonic acids are named analogously: $\text{C}_6\text{H}_5\text{SO}_2\text{NHNH}_2$, "benzenesulfonhydrazide" or "benzenesulfonylhydrazine"; $(\text{CH}_3\text{SO}_2)_2\text{NNHCH}_3$, "N,N-dimethanesulfonyl-N'-methylhydrazine."

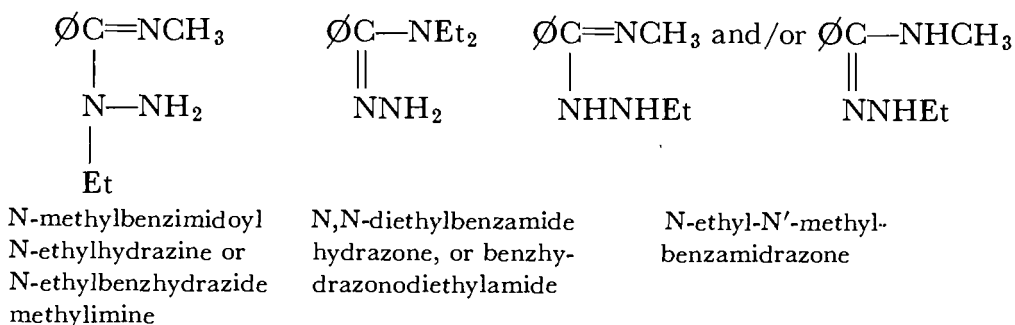
Hydrazine analogs of imidate esters, RC(OR)=NNR_2 , are most systematically named after the hypothetical enolic tautomeric form of hydrazides, called hydrazonic acids. Thus the foregoing structure with each $\text{R} = \text{CH}_3$ would be called "methyl acet-N,N-dimethylhydrazonate." The acyl chlorides, RCClNNR_2 , are named analogously as hydrazonoyl chlorides. Compounds of the type ROCR=N-N=CROR have been named as azines of the corresponding ester, or as α -alkoxyalkylidene azines.

Amidine analogs of hydrazides are known in two types, as shown, which are given the class names "amidrazones" (a contraction of amide hydrazone) and "hydrazidines" (the reader of the literature of the late 19th century must beware of the occasional use of "hydrazidine" to mean amidrazone, however). The amidrazones, of course, have two tautomeric forms in principle. All such compounds are best named as imidoyl hydrazines (or hydrazide imines), hydrazonoamides (or amide hydra-

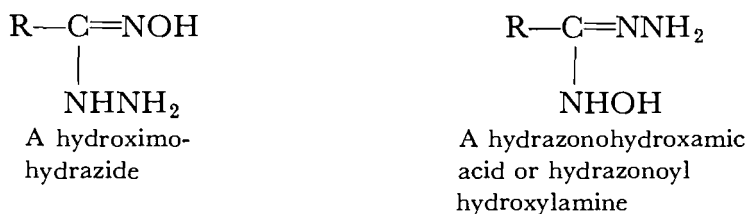


zones), and hydrazonohydrazides (or hydrazide hydrazones), as suits the structure, although when incomplete substitution makes the tautomeric form uncertain, less precise names must be used. The examples

shown serve to illustrate good practice. Compounds of the structure $\text{RC}(\text{NH}_2)=\text{N}-\text{N}=\text{C}(\text{NH}_2)\text{R}$ are called amide azines.



Substances that can be considered as the hydrazides of hydroxamic acids, or hydrazide oximes, tautomeric with hydroxamic acid hydrazone structure, or hydrazonohydroxamic acids, can be named in the foregoing manner, as N-hydroxy derivatives of amidrazones.



Hydrazides are but rarely found in nature. An example is agaritine, γ -glutamyl *p*-hydroxymethylphenylhydrazide,²¹⁴ found in the common mushroom.

PROPERTIES

Simple unsubstituted hydrazides are almost universally solids; the smaller ones, such as formhydrazide and acethydrazide, are very soluble in water, much less so in ether. Substituted hydrazides, including diacyl hydrazines, are also usually solids, although a few, such as triacetyl hydrazine, are known only as viscous oils (Table 9-2).

Benzamidrazone,²¹⁵ mp 78–79°, is the only unsubstituted, nonfluorinated amidrazone to have been isolated up to 1963. Acetamidrazone is known as its hydrochloride; the free base is apparently extremely soluble in water. Benzo-N-phenylhydrazonoamide,²¹⁶ mp 86–87°, is insoluble in water. Several tetrasubstituted amidrazones have been obtained as distillable oils.²¹⁷

Unsubstituted hydrazidines appear not to have been isolated in the free state. Acethydrazidine²¹⁸ is known in the form of its hydrochloride; it is apparently extremely water soluble as the free base. Its diphenyl

Table 9-2 *Properties of some hydrazides*

Structure	mp, °C	bp, °C/mm.
HCONHNH ₂	54	
AcNHNH ₂	67	129/18
HCONHNHCOH	159–160	
AcNHNHCOH	96	
AcNHNHAc	140*	209/15
Ac ₂ NNH ₂	132	
Ac ₂ NNHAc		180–183/15
Ac ₂ NNAc ₂	86	141/15
ØSO ₂ NHNH ₂	104–106	
ØSO ₂ NHNHO ₂ SØ	228	
ØNHN=SO	105	

* Monohydrate, mp 80–100°.

derivative,²¹⁶ acet-N-phenylhydrazonoyl N'-phenylhydrazide, appears to be insoluble in water, but it has not been obtained pure owing to rapid decomposition in the presence of air.

Benzhydroximidoyl N'-phenylhydrazide (or the tautomeric structure, benzophenylhydrazonohydroxamic acid), ØC(=NOH)NHNHØ, mp 209°, is one of the few representatives of this class of compound known.

The infrared spectra²¹⁹ of hydrazides reveal extensive hydrogen bonding except in very dilute solution. As in amides, two bands appear in the "carbonyl" region, at 1620 cm.⁻¹ and 1630–1670 cm.⁻¹. An analogous pair of bands has been reported in amidrazones,^{219c} at 1655 and 1690 cm.⁻¹, which resembles the situation with amidines.

The structures of dodecano- and isonicotino- hydrazide have been determined by X-ray crystallography.²²⁰ The O=C—N—N system is essentially planar, a situation that would be anticipated to result from extended pi-orbital overlap, analogous to amides. The C—N bond distances (1.332 Å) as well as the N—N distances (1.39–1.41 Å) are appreciably shorter than the normal single-bond distances.

All monoacyl hydrazines are weakly basic, and most of them will dissolve in dilute mineral acid. A value of 3.24 has been reported for pK_a of the acethydrazide cation,²²¹ which corresponds to a base nearly 5 powers of 10 weaker than hydrazine itself. It is obvious from this and the weak basicity of phenylhydrazine that electronic effects are strongly transmitted across the N—N single bond. Thionhydrazides are 2 to 4 powers of 10 more basic: unsubstituted examples, RCSNHNH₂, have pK_a of the cation 5 to 6; alkyl groups at the outer nitrogen increase the basicity to pK_a 6.5 to 6.7, whereas an alkyl group on the inner nitrogen increases pK_a still further, to 7.2 to 7.5.^{30b} These facts show that the cause is not

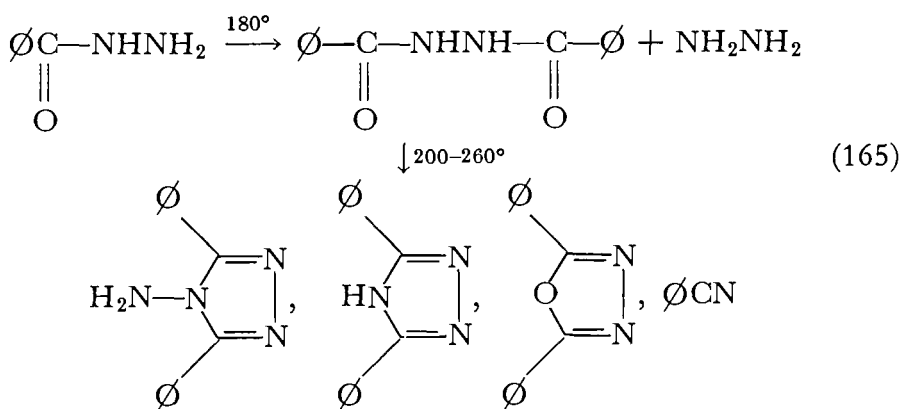
a difference in tautomeric state between ordinary hydrazides and thionhydrazides, so the difference must be attributed to the lower electronegativity of sulfur compared to oxygen.

Amidrazones and hydrazidines appear in general to be more strongly basic, although the only measurements reported ^{219c} are for the atypical case of some perfluoro acid derivatives: $\text{CF}_3\text{C}(\text{NH}_2)=\text{NNMe}_2$, K_b 9.34×10^{-11} ; $\text{C}_3\text{F}_7\text{C}(\text{NH}_2)=\text{NNH}_2$, K_b 1.74×10^{-11} ; $\text{C}_3\text{F}_7\text{C}(\text{NH}_2)=\text{NNMe}_2$, K_b 6.76×10^{-11} . Acethydrazidine ²¹⁸ is strong enough to precipitate cadmium hydroxide, but its diphenyl derivative ²¹⁶ can be precipitated from the hydrochloride by sodium carbonate.

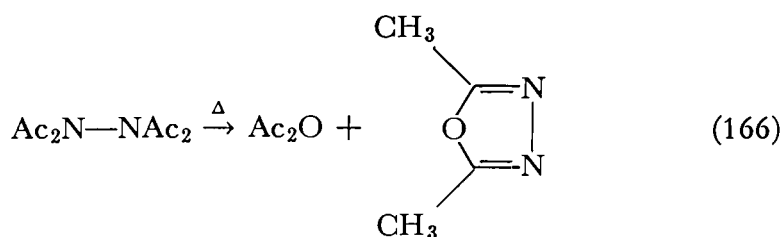
The hydrogens on the acylated nitrogens of hydrazides (i.e., the amide nitrogens) are weakly acidic; *N'*-phenylbenzhydrazide, for example, is soluble in aqueous alkali, as are secondary hydrazides and thionhydrazides. Unsubstituted thionhydrazides ^{30b} have pK_a 10.2 to 11.2; diformylhydrazine forms both a mono- and a disodium salt, and even *unsym*-diacetylhydrazine is said to form a mercuric derivative.

REACTIONS

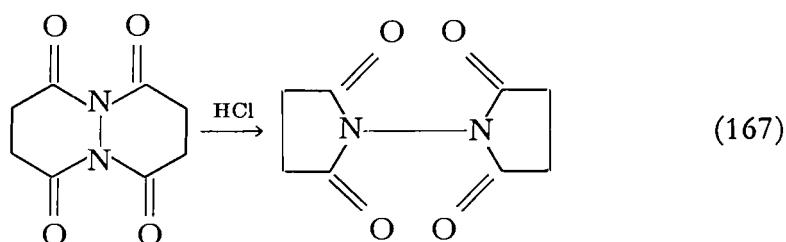
HEAT Hydrazides are usually stable to moderate heating, and, indeed, can even be prepared by controlled heating of hydrazine salts. At higher temperatures, however, usually beginning about 180° , transacylation may come into play, giving secondary hydrazides (Eq. 165). These, too, are sensitive to heat, and lose water in either of two ways, forming 4-amino-1,2,4-triazole derivatives or 1,3,4-oxadiazoles, accompanied by small amounts of N—N cleavage products. ^{222, 223} Aminotriazoles may be pre-



pared in preparatively useful yields by such reactions. Tetraacyl hydrazines are surprisingly stable to heat, and the N—N bond does not break in spite of the accumulation of electron-withdrawing substituents. Instead, elimination of an anhydride takes place, with generation of an oxadiazole ^{224, 225} (Eq. 166).

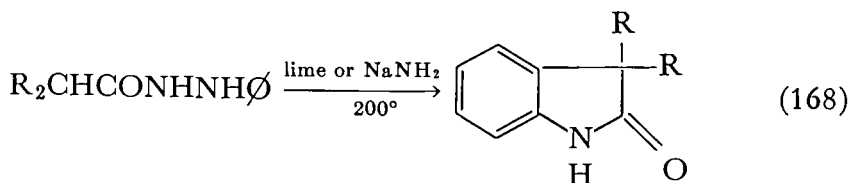


Strong acids simply form salts with monoacyl hydrazines unless the mixtures are heated for some time with water present. Acid-catalyzed acyl migration is possible with substituted hydrazides,²²⁶ including tetraacyl hydrazines (Eq. 167), but has been scarcely investigated.



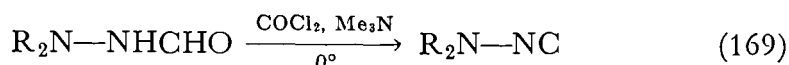
ACIDS AND BASES Hydrazides are not hydrolyzed at an appreciable rate by water alone, and even acid- or base-catalyzed hydrolysis is slow enough that salts can be prepared in water solution by reaction with mineral acids or alkalis. Hot aqueous acid slowly hydrolyzes hydrazides to carboxylic acids and hydrazine salts. Although such hydrolysis is usually quite successful with unsubstituted hydrazides, it appears that substitution may greatly retard it, for N,N'-dimethyl-N'-phenylacetylhydrazide⁶⁸ resisted all attempts at hydrolysis. Hydrolysis by hot aqueous alkali is also usually successful, although it is sometimes diverted partly or entirely to oxidation-reduction reactions.²²⁴ This behavior is especially typical of sulfonyl hydrazines, and will be taken up in more detail in the discussion of oxidation and reduction, further ahead. Enzymic hydrolysis of hydrazides has also been observed, as in the action of α -chymotrypsin on tyrosine hydrazide.

A strong base without water may catalyze condensation reactions, especially with phenylhydrazides. Oxindoles are formed by such means²²⁸ (Eq. 168), in a reaction reminiscent of the Fischer indole synthesis.

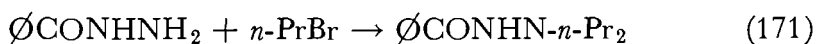
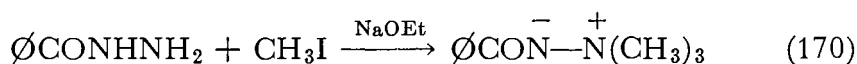


Formhydrazides bearing a hydrogen on the acylated nitrogen may be dehydrated²²⁹ in a manner similar to formamides; the products are

isocyanoamines (Eq. 169). The dehydrating agents are acid chlorides, such as phosphoryl chloride or phosgene, in the presence of tertiary amines.

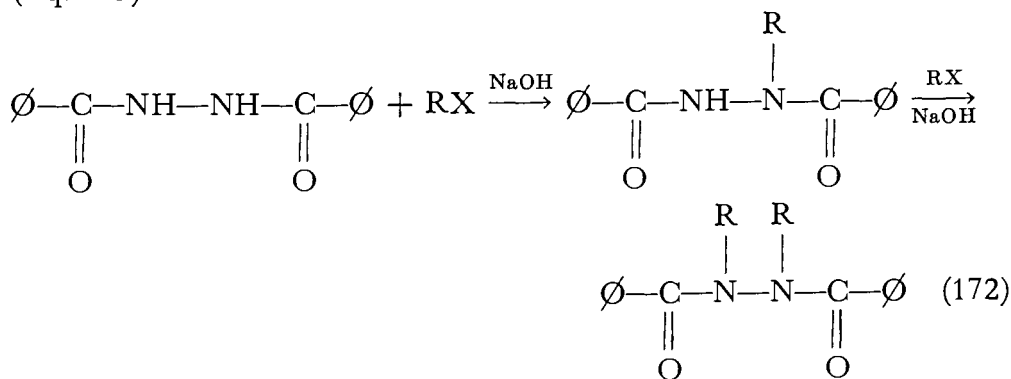


ALKYLATION Hydrazides are susceptible to alkylation in the neutral state, when the nonacylated nitrogen is attacked, or as their anions, which may become alkylated at the acylated nitrogen. These facts are, of course, the expected consequence of the relative nucleophilicity of the two hydrazine nitrogens in the respective forms. Understandably, only monoacyl hydrazines are ordinarily alkylatable in the neutral state. With methyl iodide, substitution usually continues at the same nitrogen until it is quaternized²³⁰; the product of such a process is commonly isolated as an amine imide inner salt, isoelectronic with amine oxides (Eq. 170). Larger alkyl groups are of course more subject to steric

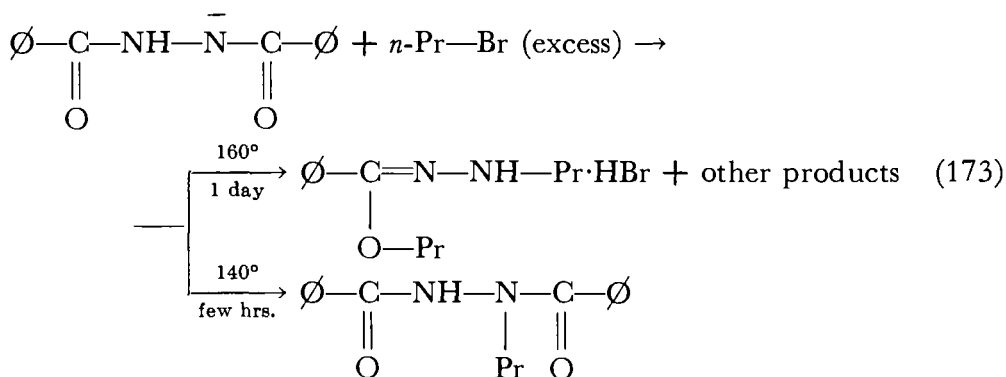


effects (Eq. 171), and alkylation with them does not usually reach the quarternary stage. The amine imides may undergo rearrangement on heating, analogous to the Stevens rearrangement (cf. Chapter 2), involving a shift of a substituent from the quaternary to the imide nitrogen; such migration has been observed only with benzyl groups.^{230b}

The sodium salts of monoacyl hydrazines appear to be at least as readily alkylated at the N' position as at the anionic nitrogen, for even the sodium salt of N',N'-dimethylbenzhydrazide is converted to the N',N',N'-trimethyl derivative.^{230a} It is only when the N'-nitrogen carries a base-weakening substituent, such as a phenyl or another acyl group, that alkylation of the anionic nitrogen becomes exclusive. The most important use of the reaction is in the preparation of *sym*-disubstituted hydrazines by alkylation of diacyl hydrazines,^{105, 231} although alkylation can be stopped at the monoalkyl stage by use of the monosodium salts^{231c} (Eq. 172).

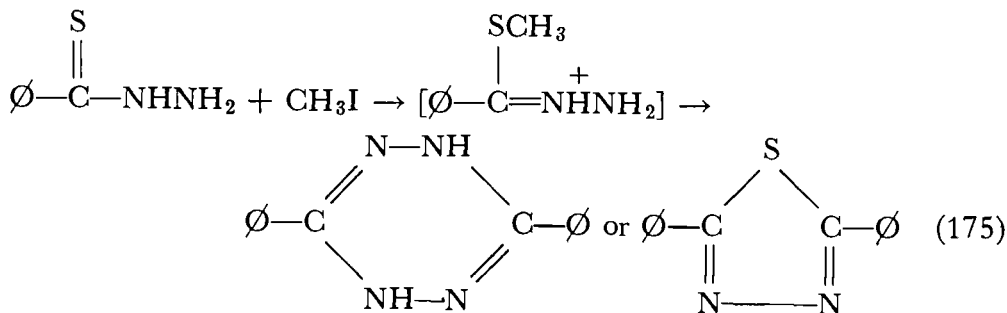
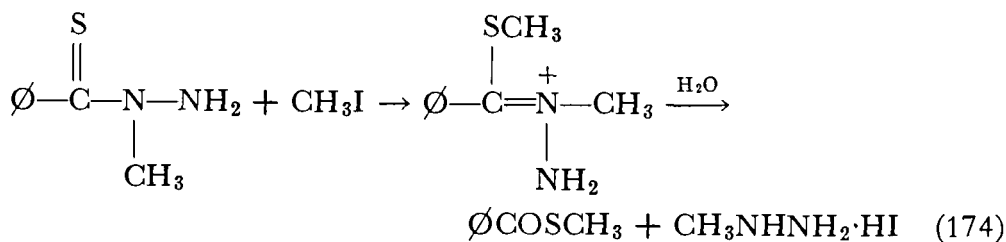


In one isolated case, treatment of the monosodium salt of *sym*-dibenzoyl hydrazine with an alkyl halide, under conditions close to forcing (160° , 1 day), has led to the introduction of an O-alkyl group as well ^{231c}; at 140° , only normal, monoalkylation occurred (Eq. 173). The yield was low, and the mechanism of the reaction is not clear, but it does not seem unlikely that the O-alkylation resulted from reaction of the neutral hydrazide after the first alkyl group had replaced the sodium. It can be said



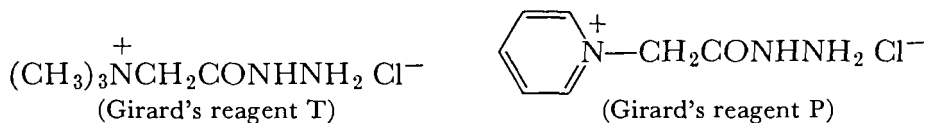
that, in general, diacyl hydrazines that already bear one alkyl group are not readily alkylated further unless the alkyl groups are both methyl or the second stage is intramolecular, forming a pyrazolidine or piperidine ring.

Thioacyl hydrazines react with methyl iodide preferentially at the sulfur atom, giving thiolhydrazone esters or their transformation products ²³² (Eqs. 174, 175).



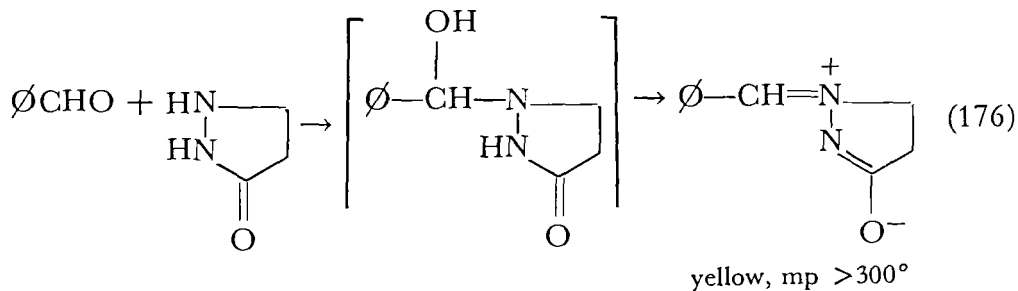
ALDEHYDES AND KETONES Hydrazides having an unsubstituted amino group, RCONRNH_2 , react more or less readily with all but highly hindered aldehydes and ketones to produce hydrazones of the type $\text{RCONRN}=\text{CR}_2$; the acylated nitrogen need not be otherwise substituted. This reaction is, of course, a familiar one for making crystalline derivatives of aldehydes and ketones, and is particularly widely used with the hydrazide of carbamic acid, commonly known as semicarbazide. The nature of the hydrazone-forming reaction³⁹ has already been discussed (p. 130).

There are several special applications of the formation of hydrazones from hydrazides. Hydrazides bearing a quaternary ammonium function²³³ in addition were introduced in 1936 as reagents for converting aldehydes and ketones into water-soluble salts, of value for extracting



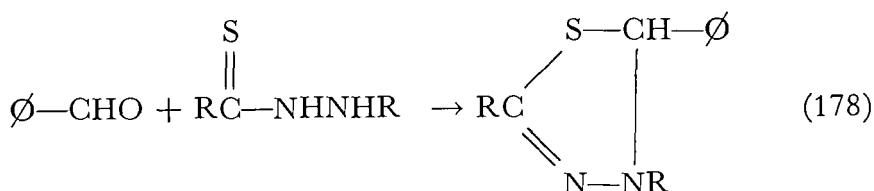
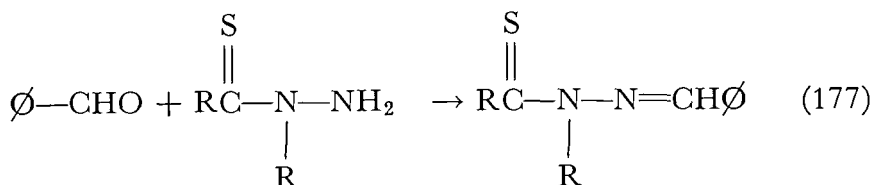
such compounds from complex mixtures. Such hydrazides are usually called "Girard's reagents"; the two commonest are shown. Hydrazides containing an asymmetric center have been used in resolving suitable aldehydes and ketones into their enantiomers. Examples are 5-(α -phenylethyl)-semioxamazide,²³⁴ $\text{OCH}(\text{CH}_3)\text{NHCOCOCONHNH}_2$, and 1-mentohydrazide.²³⁵

It is ordinarily assumed, with some justification, that hydrazides substituted at the N' -position will not react with aldehydes and ketones, since hydrazone formation is then not structurally possible. It does not seem unlikely, however, that reactive aldehydes would be able under suitable conditions to form analogous compounds to carbinolamines. In one interesting case,⁴⁰ such an adduct apparently undergoes dehydration (Eq. 176) even though a conventional hydrazone cannot form; the generality of this behavior has not been explored.



Thioacyl hydrazines having an unsubstituted $-\text{NH}_2$ group form hydrazones normally (Eq. 177), but N' -substituted compounds also

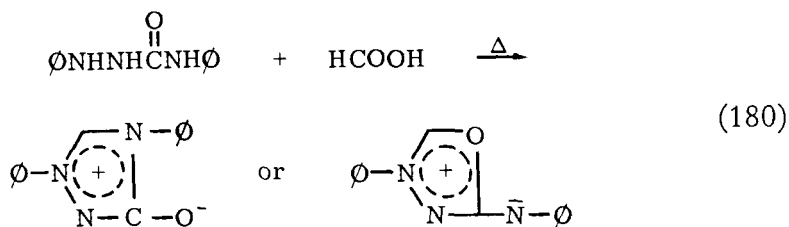
react by addition and dehydration²³² (Eq. 178). The products are thiadiazolines.



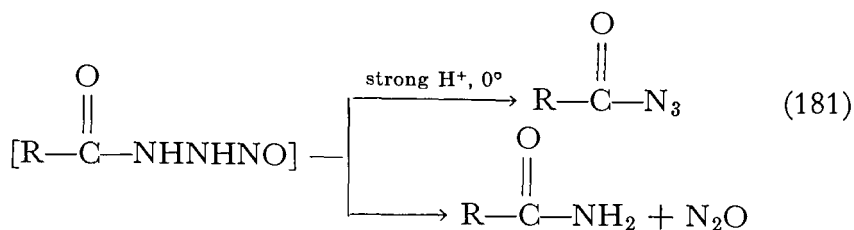
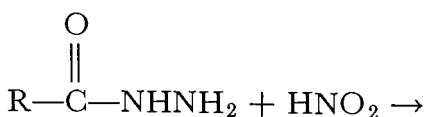
ACYLATION Monoacyl hydrazines are easily acylated to *sym*-diacyl hydrazines if there is a hydrogen on the N'-position (Eq. 179). Esters are too mild to accomplish this readily, but acid chlorides are so effective that it is difficult to stop the acylation of hydrazine with them at the monoacyl stage.²³⁶ Further acylation is more difficult, but has been carried even to the tetraacyl stage by heating with acetic anhydride.²²⁵



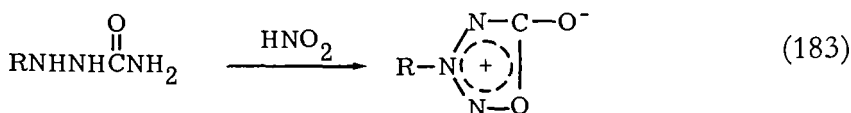
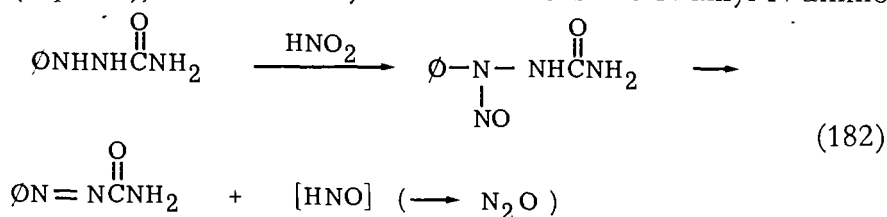
An unusual case of acylation is the action of formic acid on 1,4-diphenylsemicarbazide; the presumed intermediate formyl derivative undergoes dehydrative cyclization to form a mesoionic ring system²³⁷ (Eq. 180).



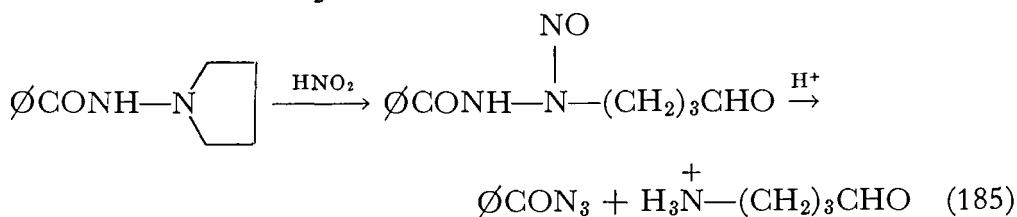
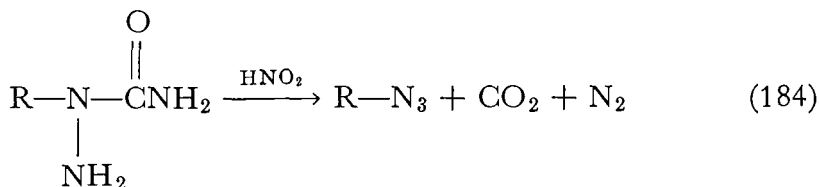
NITROSATION Hydrazides can also be acylated by the common inorganic acylating agents. Nitrosation of unsubstituted hydrazides is certainly the most commonly encountered example of such reactions, for it is widely used for preparing acid azides for use in the Curtius rearrangement.²³⁶ It is commonly carried out in strong acid near 0°, and under these conditions usually gives very high yields (Eq. 181). There is, however, a side reaction that can become important when other conditions are used, involving N—N cleavage to give the amide and nitrous oxide.²³⁸ Both types of product are believed to arise from the N'-nitroso hydrazide. Substituted hydrazides can also be nitrosated. The N-nitroso compounds produced can often be isolated, but they are rather labile if a hydrogen is present on an adjacent nitrogen and form azo compounds by



elimination of nitroxyl ²³⁹ (Eq. 182). 1-Alkyl semicarbazides consume two moles of nitrous acid and become converted to mesoionic oxatriazoles ^{240a} (Eq. 183), whereas 2-alkyl semicarbazides and N-alkyl-N-amino

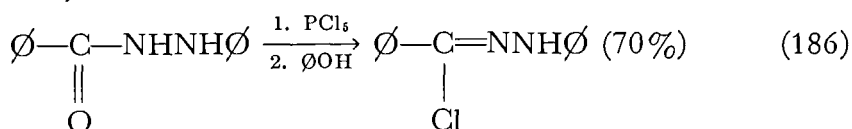


urethans are converted to alkyl azides ⁹⁰ (Eq. 184). Hydrazides of the type $\text{RCONH}-\text{NR}_2$ undergo nitrosative dealkylation analogously to tertiary amines ^{240b} (Eq. 185).

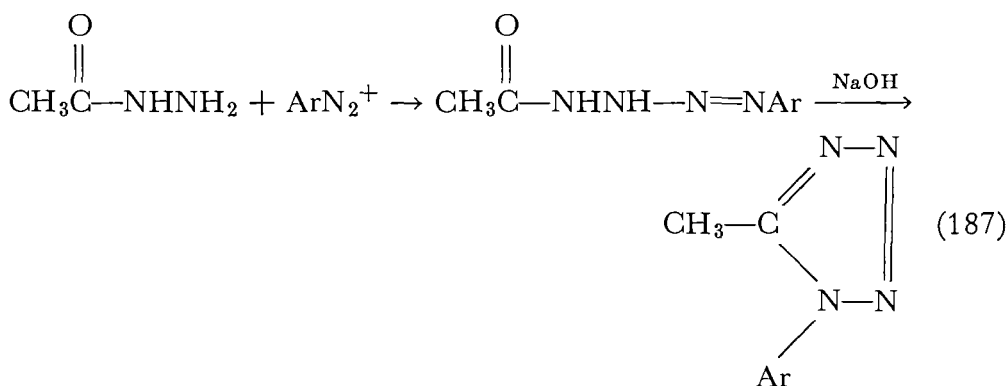


Just as phosphorus pentachloride converts monosubstituted amides to imidoyl chlorides, so does it convert N'-substituted hydrazides to hydrazonoyl chlorides.²⁴¹ The initial product, however, may be a phosphorylated substance; in the case of N'-phenylbenzhydrazide, controlled solvolysis with phenol in ether releases the hydrazonoyl chloride (Eq. 186), which is obtained in good yield, accompanied by minor amounts of N-phenyl-N,N'-dibenzoylhydrazine and phosphorus-containing substances. N-

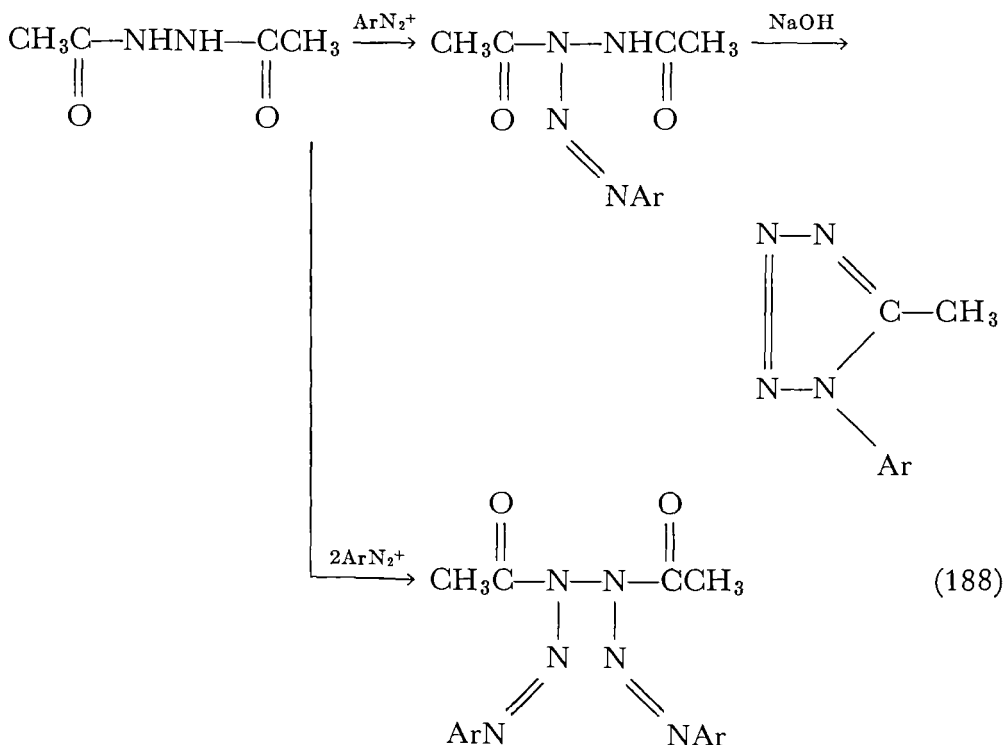
Acylation with chlorides of organic phosphorus acids parallels the reactions of ordinary acid chlorides.²⁴²



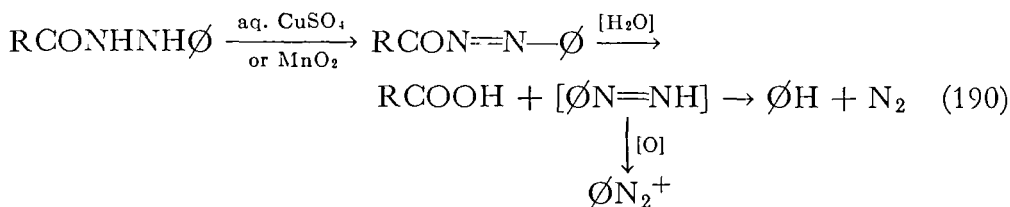
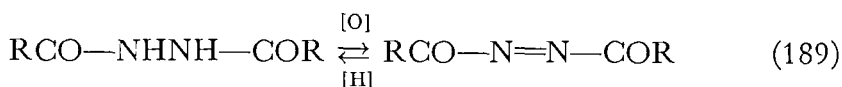
DIAZONIUM COUPLING In addition to the foregoing types of electrophilic attack on hydrazides, there remains the case of diazonium coupling, which with monoacyl hydrazines takes place at the more basic, N', nitrogen.²⁴³ These coupling products are cyclized to 1,5-disubstituted tetrazoles by alkali if there are no other N-substituents (Eq. 187). Secondary hydrazides behave similarly, an acyl group being expelled by the cycliza-



tion processes²⁴⁴ (Eq. 188). With an excess of diazonium salt, diacyl hexazadienes are formed.

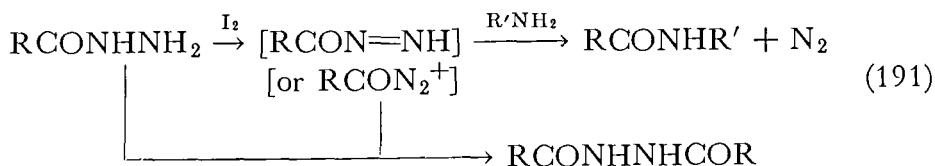


OXIDATION Hydrazides are most susceptible to oxidation when there are hydrogens on adjacent nitrogens. Under these circumstances, various oxidizing agents, such as halogens, cupric salts, mercuric oxide, and potassium ferricyanide, effect conversion to azo compounds, and Fehling's and Tollens' reagents are reduced. The azo compounds are usually isolable when both nitrogens bear a substituent, as in secondary hydrazides²⁴⁵ (Eq. 189). N'-Phenyl hydrazides readily break up on oxidation in aqueous medium, forming the carboxylic acid and benzene (or products



derived from oxidation to the diazonium ion; Eq. 190), a reaction that has found application in peptide chemistry as a mild means of removing a protective group.²⁴⁶ Oxidation of secondary hydrazides with oxygen in alkaline solution produces carboxylate salts and nitrogen, usually accompanied by light emission. This is the basis of the well-known luminol reaction; the luminescence has been identified as arising from an excited state of the carboxylate product.²⁴⁷

Unsubstituted hydrazides presumably also give azo compounds on oxidation; the reaction mixtures behave as powerful, but unstable, acylating agents, which may be acyl diimides or acyl diazonium ions. When the oxidizing conditions are mild and slow, as with iodine or peroxy acid as oxidizing agent, the intermediate reacts with as yet untouched hydrazide to produce a secondary hydrazide.^{61, 248} If more active nucleophiles, such as amines, are present during the oxidation, these are acylated instead (Eq. 191), and so efficient is the overall process that it has been successfully applied to peptide synthesis.^{248b} Under other conditions, the acyl diimide appears to decompose intramolecularly, for the

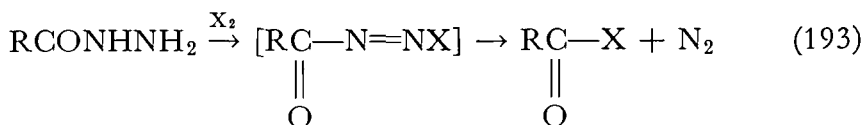


principal products become an aldehyde and nitrogen²⁴⁹ (Eq. 192).



This is a variant of the well-known McFadyen-Stevens aldehyde synthesis, which is more commonly carried out by an internal oxidation process

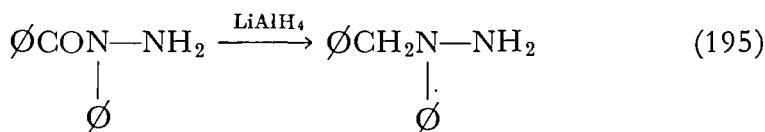
through alkaline decomposition of N' -benzenesulfonyl hydrazides ^{70, 250} (see ahead). When oxidation of unsubstituted hydrazides is carried out with halogen (or S_2Cl_2) in nonaqueous medium, the corresponding acyl halide is produced (Eq. 193), perhaps through an unstable acyl diazo-halide.²⁵¹ This reaction also occurs with sulfonyl hydrazines.^{251c} The fact that bromine oxidizes sulfonyl hydrazines in hydrochloric acid solu-



tion only to sulfonyl bromide, free of sulfonyl chloride (Eq. 194), is taken as evidence that a free cation, $ArSO_2N_2^+$, is not involved.



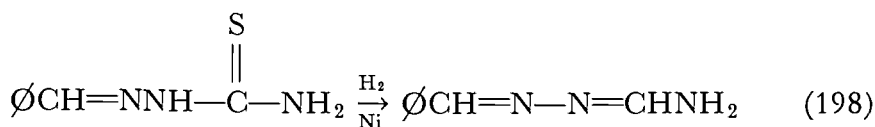
REDUCTION The reduction of hydrazides has been accomplished principally with lithium aluminum hydride; the products are hydrazines.^{80, 112, 114, 119} The reaction seems to be fairly general, regardless of presence of alkyl or aryl groups on nitrogen (Eqs. 195, 196). Some failures,^{252a} notably benzhydrazide and its N',N' -dimethyl derivative, have been attributed to interference by the acidic amide $N-H$, but the successful reduction of N',N' -dimethylformhydrazide¹¹⁹ and of some



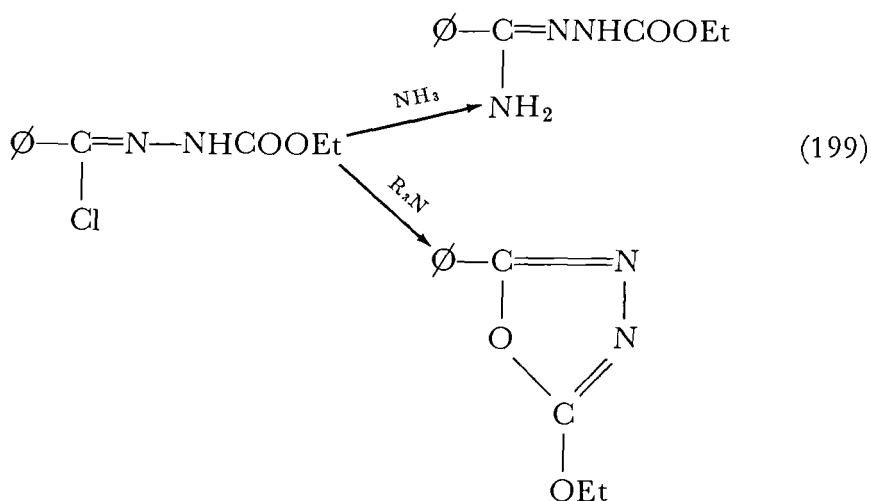
N' -phenylhydrazides¹¹⁴ casts doubt on this explanation; perhaps it is a question of the solubility of metallic derivatives first formed. Sodium amalgam with acetic acid in ethanol has not unexpectedly been observed to cleave the $N-N$ bond, giving an amide. Cleavage of the $N-N$ bond has also been accomplished with hydrogen and Raney nickel²³⁰ (Eq. 197). On the other hand, a thiosemicarbazone has been desulfurized



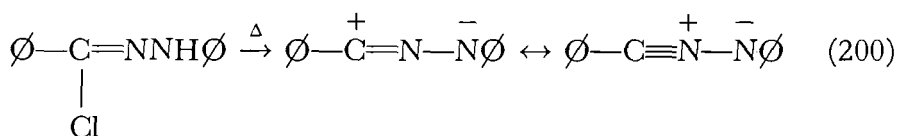
to a formamidrazone derivative without $N-N$ cleavage^{252b} (Eq. 198).



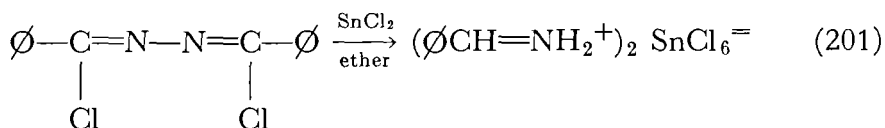
HYDRAZONOYL HALIDES The chemistry of the hydrazonoyl halides, $RCX=NNHR'$, is characterized by displacement of X by nucleophiles, often with subsequent cyclization,^{173-175, 241a, 253a} (Eq. 199), and by elimination of HX. In the case of benzo-N-phenylhydrazonoyl chloride, the result of heating is the loss of hydrogen chloride (Eq. 200) and the



formation of what have been called "isodiazo alkanes,"^{253b} more properly,



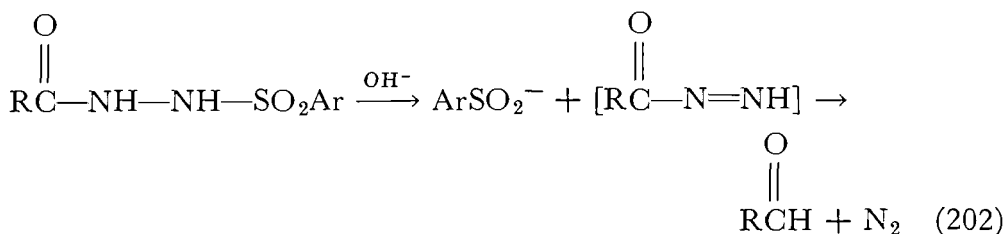
nitrile imines. Hydrazonoyl chlorides are reduced by ethereal stannous chloride, just as are imidoyl chlorides (Sonn-Müller reaction), but in addition the N—N bond is cleaved, giving aldimine chlorostannates²⁵⁴ (Eq. 201).



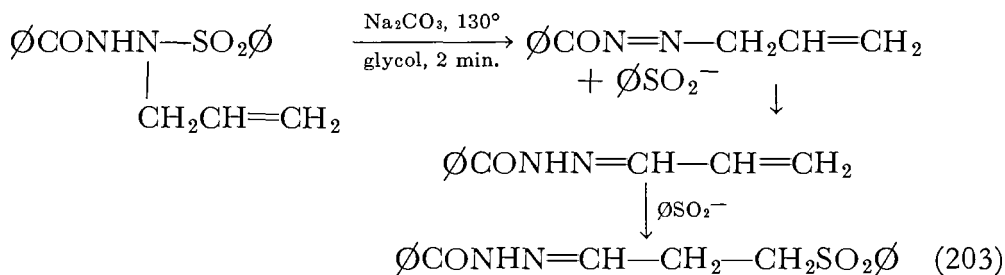
HYDRAZONATE ESTERS The esters of hydrazonic acids^{231c, 253a} have not been extensively studied; little more can be said of them other than that they are basic, as would be expected from their close structural relationship to the imidate esters, and that they appear to be somewhat less reactive. Rearrangement to N-substituted hydrazides, analogous to the Chapman rearrangement, has not been reported.

SULFONHYDRAZIDES The chemistry of sulfonyl hydrazines, to the extent that it does not parallel that of ordinary hydrazides, is dominated

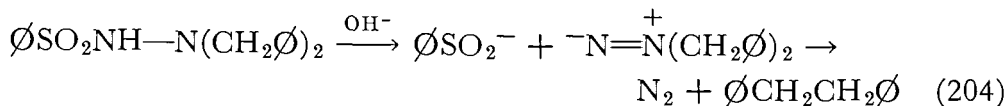
by the case with which the elements of sulfinic acid are eliminated, especially in basic medium, resulting in oxidation of the hydrazine moiety. The role of sulfonyl hydrazines in the McFadyen-Stevens⁷⁰ aldehyde synthesis²⁵⁰ has already been alluded to; the acidity of the hydrazide hydrogens promotes the elimination, with the presumed intermediate formation of an acyl diimide, which decomposes to nitrogen and an aldehyde (Eq. 202). An unusual case is the behavior of N'-allyl-N'-



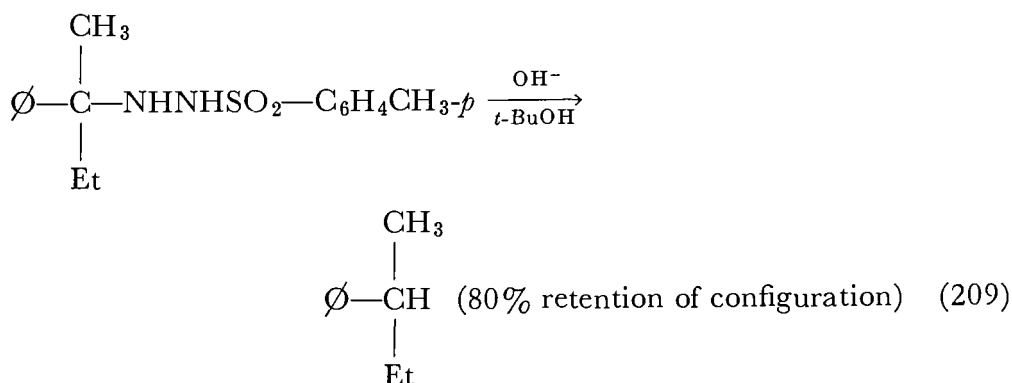
benzenesulfonylbenzhydrazide,^{255a} which undergoes rearrangement with migration of the benzenesulfonyl group. It is believed to begin by the usual elimination, followed by tautomerization to acrolein benzoylhydrazone, to which the eliminated benzenesulfinate ion again adds (Eq. 203).



Elimination occurs even when an azo structure is excluded, as in N',N'-disubstituted sulfonylhydrazides, if there is a hydrogen on the nitrogen bearing the sulfonyl group. The products obtained depend not only on the nature of the N'-substituents, but strongly on the environment. Azamines are presumably formed initially under all circumstances; if the structure of the N'-substituents is such as to promote free-radical formation, combination of the substituents accompanied by loss of nitrogen occurs, just as in the oxidation of *unsym*-disubstituted hydrazines (see p. 136). N',N'-Dibenzylbenzenesulfonylhydrazide, for example,^{56, 63} is converted to dibenzyl (Eq. 204); N-benzenesulfonylamidopyrrolidine, however, gives two molecules of ethylene rather than cyclobutane.⁶⁰

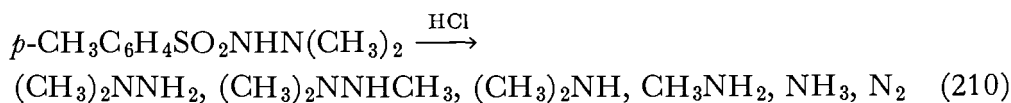


tertiary butyl alcohol as a solvent, the reaction shows a high degree of

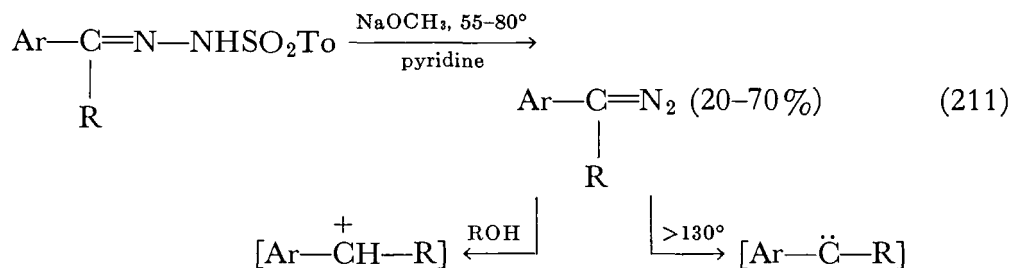


stereospecificity, which has been interpreted as electrophilic displacement of N_2 by H^+ in a frontal attack.⁴⁸

Decomposition of sulfonylhydrazides has occasionally been observed in acid solution as well.³⁶ The products are those that might be expected of an azaminium (diazonium) salt first formed (Eq. 210).



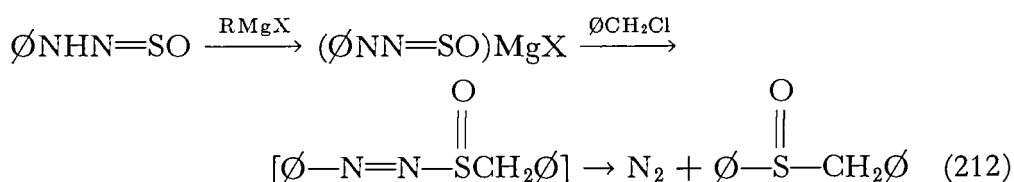
Sulfonylhydrazones undergo 1,1-elimination of sulfinic acid through their salts also. The derivatives of aromatic ketones and aldehydes and the monohydrazones of *vic*-diketones in general undergo such elimination at temperatures low enough that diazoalkanes can be isolated in moderate yield²⁵⁸ (Eq. 211); this is known as the Bamford-Stevens reaction, and accomplishes the same result as the oxidation of unsubstituted hydrazones



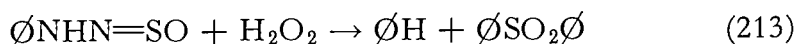
somewhat more reliably. The hydrazones of aliphatic ketones and aldehydes generally require higher temperatures ($130-150^\circ$) for decomposition, and the diazoalkanes then decompose as fast as they are formed, giving azines and other products derived from the corresponding carbenes^{259a} (see Chapter 10). Photolysis of salts of tosylhydrazones also converts them to carbene-derived products.^{259b} A reaction path leading to products derived from the corresponding carbonium ion always com-

petes more or less significantly with the Bamford-Stevens reaction when a sodium alkoxide is used as the base, and, indeed, this path can be made the major reaction in protic solvents, such as alcohols.²⁶⁰ It presumably occurs through proton transfer from the alcohol to the diazoalkane in the hot solution; this reaction can be repressed by using aprotic solvents, such as pyridine or glycol ethers, or by using butyllithium at depressed temperatures to form the salt.

THIONYL HYDRAZINES As a class, thionyl (sulfinyl) hydrazines,³⁵ $R_2N-N=SO$, have been relatively little studied. The acidic hydrogen of thionyl phenylhydrazine allows sodium or magnesium salts to form. Treatment of such salts with benzoyl chloride brings about deep-seated decomposition. Alkylation probably takes place at sulfur, for treatment with benzyl chloride leads to phenyl benzyl sulfoxide, which is a likely product of the decomposition of a phenylazo sulfoxide (Eq. 212) (thionyl *N*-phenyl-*N*-benzylhydrazine, prepared in another way, is stable). Grignard reagents merely form salts with monosubstituted thionyl hydra-



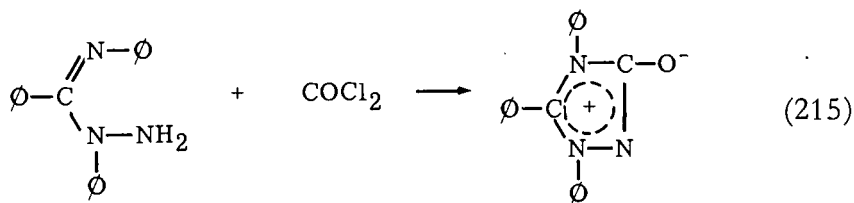
zines, whereas disubstituted ones are unreactive. Oxidation of thionyl phenylhydrazine gives benzene and diphenyl sulfone, whose formation seems most simply explained by initial attack on sulfur to form an azo sulfinic acid (or a tautomer) (Eq. 213). Reduction with sodium under warm toluene follows a somewhat analogous path, thiophenols being



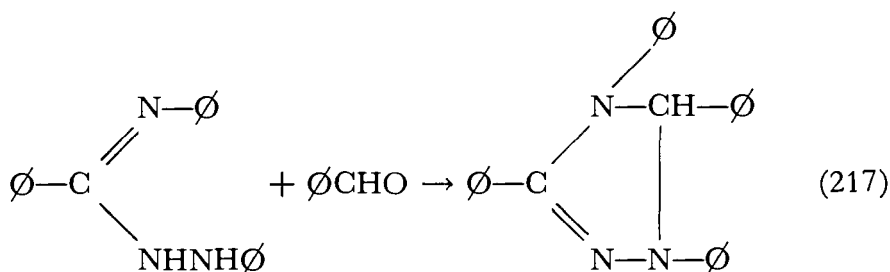
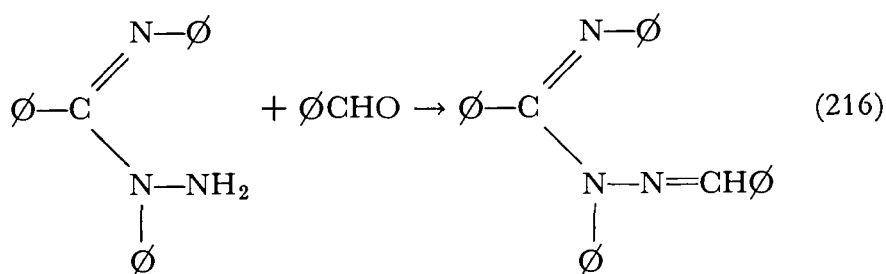
formed presumably through an arylazothiol (or tautomer)²⁶¹ (Eq. 214).



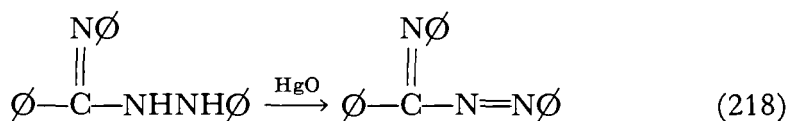
AMIDRAZONES The reactions of amidrazones have been relatively little studied. They are easily converted to triazoles through their acyl derivatives if not fully substituted²⁶² (Eq. 215). A free NH_2 on the



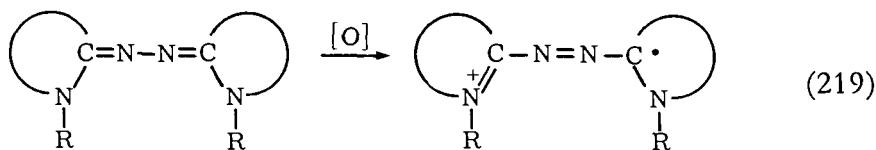
hydrazine moiety allows for rapid hydrazone formation, whereas the isomeric arrangement leads to formation of triazolines with benzaldehyde, noticeably less easily than hydrazone formation^{237b} (Eqs. 216, 217).



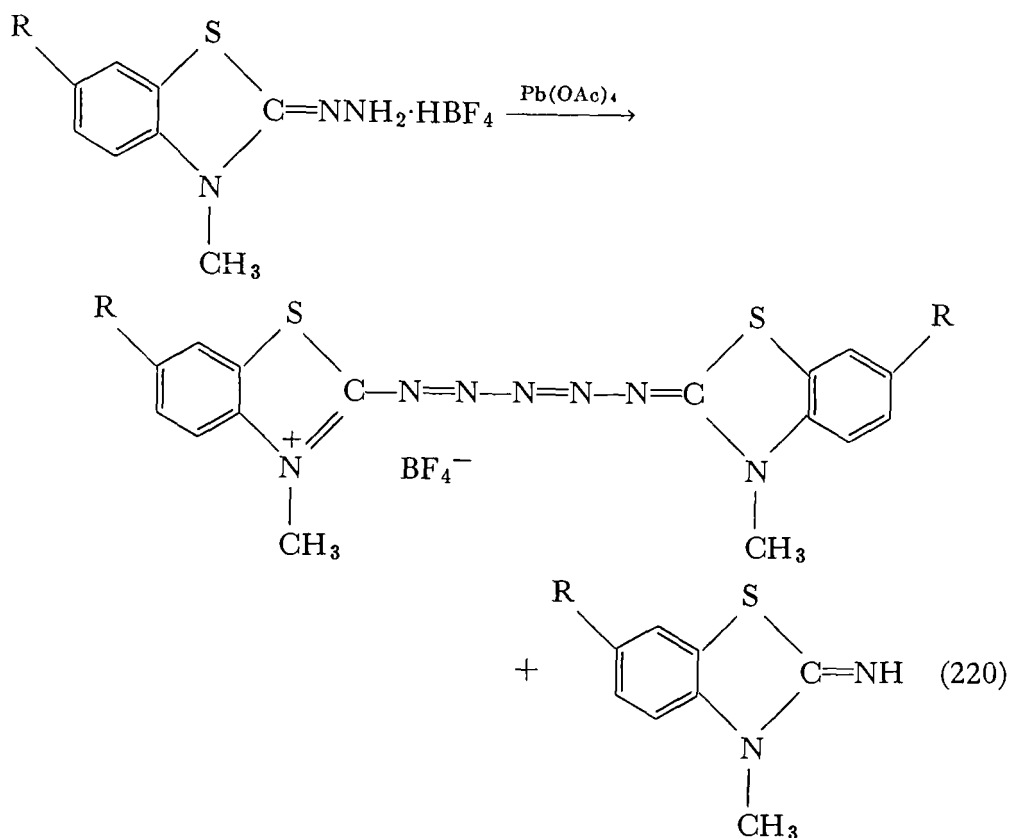
Amidrazones having an $-\text{NHNH}-$ structure are readily oxidized to azo compounds (Eq. 218), but the structure $\text{RC}(=\text{NR})\text{NRNH}_2$



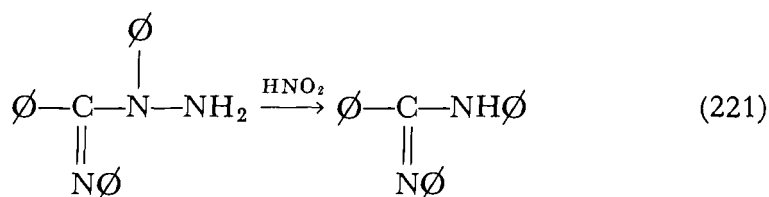
is inert.^{237b} Amidrazones of the amide azine type, however, can be oxidized by a one-electron step to cation radicals, whose salts are intensely colored (generally violet) and can be isolated²⁶³ (Eq. 219).



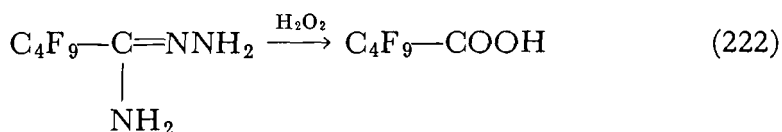
Aminoguanidine as well as cyclic amidrazones having an unsubstituted hydrazono moiety can be made to undergo oxidative coupling with phenols, aromatic amines, and active methylene compounds to form azines or azo compounds having dyestuff properties,⁶⁵ analogous to the oxidative coupling of *unsym*-disubstituted hydrazines (see p. 137). Oxidation in the absence of a coupling agent has led to pentazadienes related to the cyanine dyes (Eq. 220). These reactions presumably



take place through azo or azaminium intermediates. Nitrous acid converts terminally unsubstituted amidrazones to amidines (Eq. 221), analogous to the behavior of other hydrazine derivatives with the N—NH₂



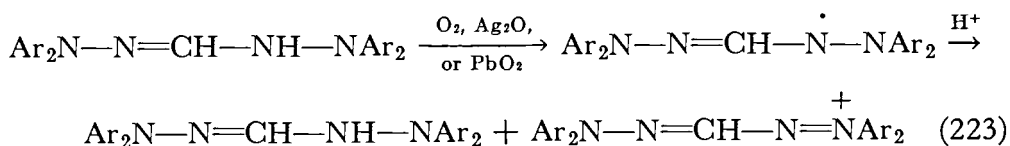
structure.^{237b} Perfluorovaleramidrazone is converted to perfluorovaleric acid by hydrogen peroxide (Eq. 222); this is perhaps an oxidation process,



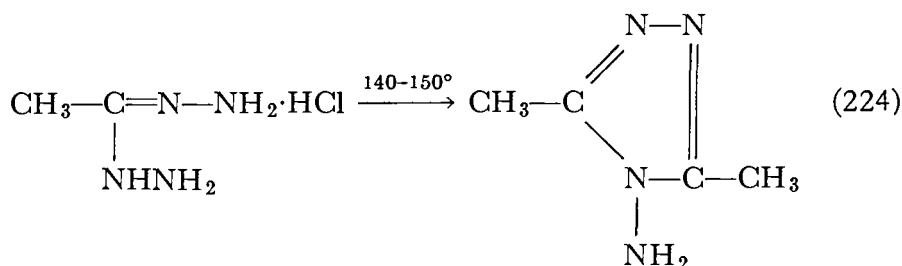
since hydrolysis does not take place in the absence of peroxide.^{219c}

HYDRAZIDINES The chemistry of the hydrazidines has been even less studied than that of the amidrazones. They are easily oxidized, and in some instances the free bases are rapidly attacked by air.²¹⁶ Certain

tetraaryl hydrazidines have been oxidized to blue-green free radicals, which are isolable, but disproportionate in contact with acids into the parent hydrazidine and a formazan derivative ²⁶⁴ (Eq. 223). Elimination



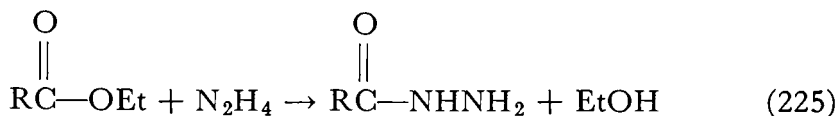
of hydrazine can evidently take place, for acethydrazidine hydrochloride is reportedly converted to a 4-amino-1,2,4-triazole on heating ²¹⁸ (Eq. 224).



Reduction to amidrazones has also been reported.^{216, 265} Some acyl derivatives have been cyclized to 4-amino-1,2,4-triazolones by heating with acid or base.¹⁸⁹

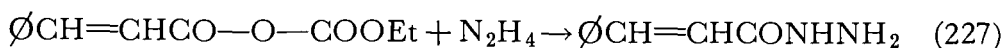
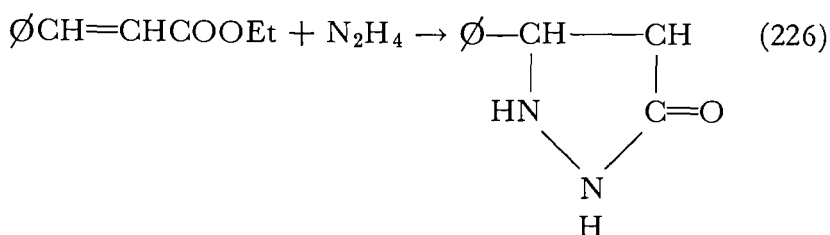
PREPARATIVE METHODS

CARBOHYDRAZIDES The usual way to prepare unsubstituted hydrazides is the acylation of hydrazine (or its hydrate) with esters ²³⁶ (Eq. 225). With unhindered esters, such reactions take place readily on short refluxing, and are in some cases spontaneous and exothermic. Although esters have the advantage of seldom producing diacyl hydrazides, the less reactive ones may require inconveniently long reaction times or undesirably



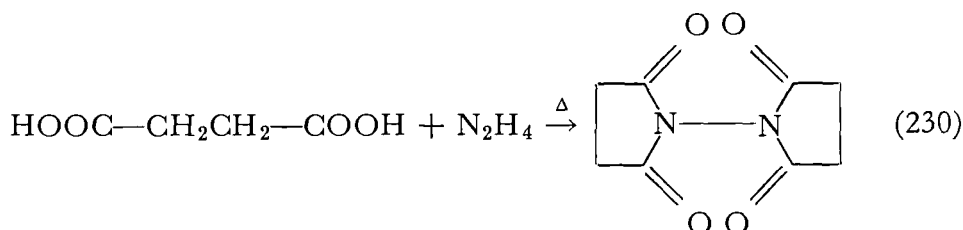
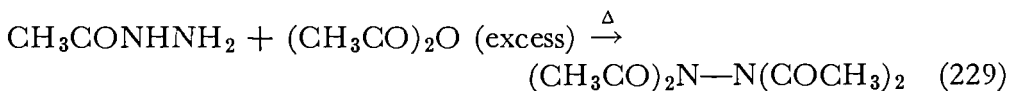
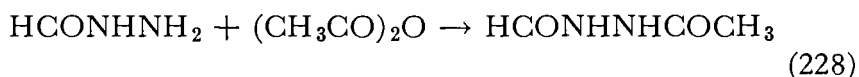
severe conditions. Ethyl cinnamate, for example, undergoes ring closure when it is heated with hydrazine, giving a pyrazolidone (Eq. 226); the hydrazide is obtained by the use of a more active acylating agent ^{266a} (Eq. 227).

Anhydrides, acid chlorides,^{266b} acyl azides, and acyl imidazoles ^{266c} also give hydrazides by reaction with hydrazine. Acid chlorides are so reactive that it is difficult to stop the reaction short of diacylation. This

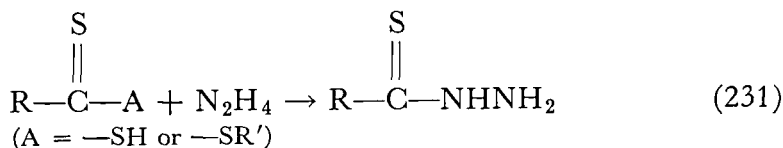


group of acylating agents is more vigorous than esters, and may become useful when esters are unsatisfactory. It is also possible to prepare hydrazides by heating hydrazine salts of carboxylic acids ^{226, 267}; yields may be high with unhindered acids free of other reactive centers. A more complete discussion of the conversion of carboxyl derivatives to hydrazides is available elsewhere.²³⁶

Diacyl, triacyl, and tetraacyl hydrazines are prepared by further acylation of primary hydrazides, usually with acid chlorides or anhydrides ²²¹ (Eqs. 228, 229), although in the especially favorable case of succinic acid, a tetraacyl hydrazine has been obtained by heating the hydrazine salt ²²⁶ (Eq. 230).

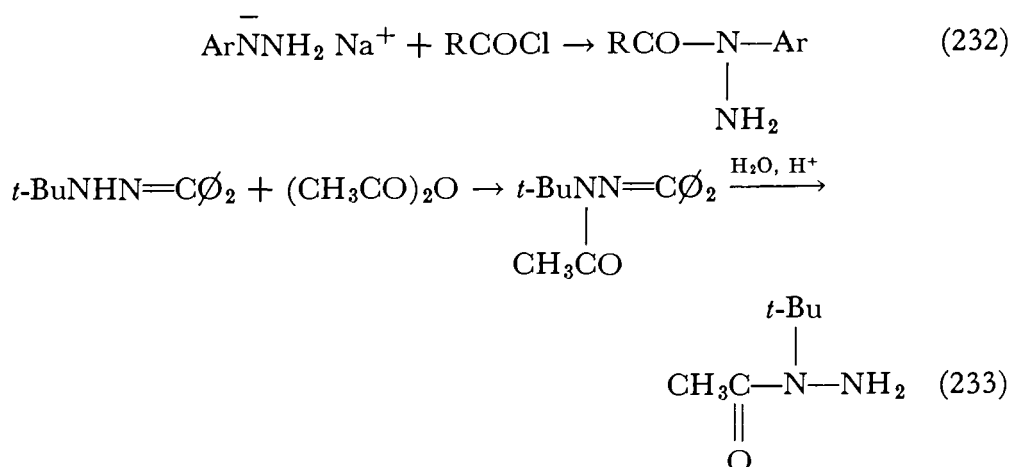


Thionhydrazides are obtained by thioacylation of hydrazine with dithio esters or acids ^{30b} (Eq. 231).

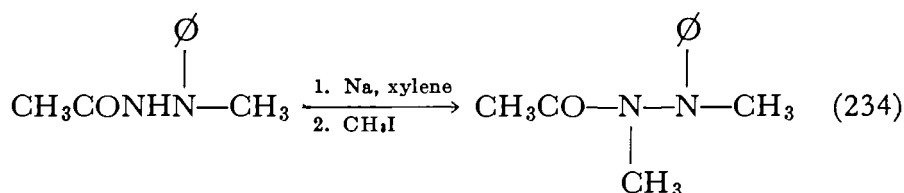


Substituted hydrazides may also be obtained by acylation procedures, as described in earlier sections (Eqs. 12, 13). The site of acylation of unsymmetrically substituted hydrazines depends on both steric and electronic factors.³⁰ When the acyl group enters at an undesired location,

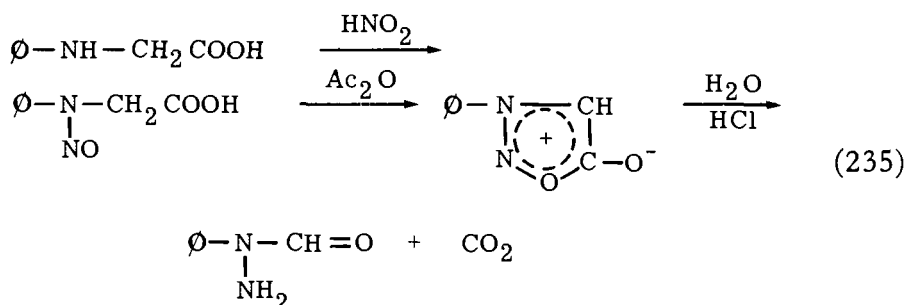
the result may often be altered either by the use of blocking agents (acylation of hydrazones²⁷) or by acylating metallic salts of hydrazines²⁶⁸ (Eq. 233).



Substituted hydrazides can also be obtained by alkylation of simpler hydrazides or their metallic salts^{103, 230, 231} (Eq. 234), as has been described in the foregoing section.

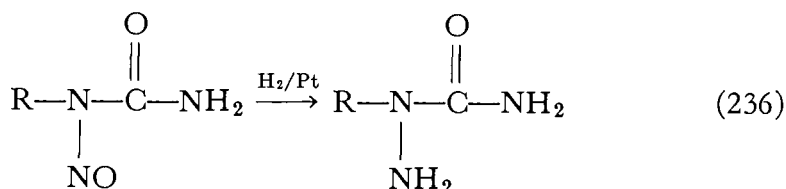


A useful method of synthesizing N-substituted hydrazines is the hydrolytic ring opening of sydnone (Eq. 235), which are easily prepared from N-substituted glycines.²³⁷



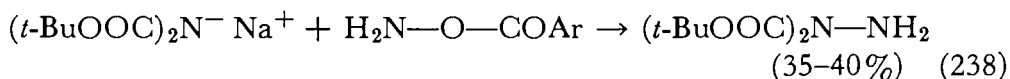
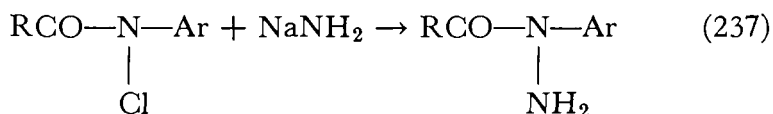
Oxidative methods are not important in the preparation of hydrazides, although it is possible to make them that way. The route involves the reaction of aldehyde hydrazones with oxygen²⁶⁹ or halogen^{173–175} and hydrolysis of the resulting hydrazonoyl derivatives (Eq. 141). Reduction is of significance only with N-nitroso or N-nitro amides, which are of

considerable importance in the preparation of semicarbazides ^{84, 85, 240b, 270} (Eq. 236). Reduction of acyl azo compounds also gives hydrazides, but since the azo compounds must usually be prepared from the hydrazide in the first place, the process is not of preparative value. Half hydrazides of carbonic acid (amino urethans or carbazate esters) are available in



considerable variety through various addition reactions of azodicarboxylic ester.^{104, 271} The products are N,N'-dicarboethoxy hydrazines, but one carboethoxy group can be reduced to a methyl group in some cases ¹¹² (cf. Chapter 11).

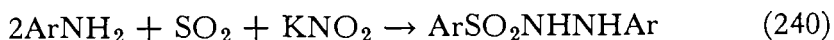
A method of use primarily in structure proof is the amination of N-haloamides with sodamide ²⁶⁸ (Eq. 237). Amination of imides through reaction of their sodium salts with O-acyl hydroxylamines (Eq. 238) is of use in special cases.²⁷²



HYDRAZIDES OF SULFUR ACIDS Sulfonyl hydrazines are almost always prepared by the acylation of hydrazines with sulfonyl chlorides (Eq. 239); esters cannot be used, since alkyl sulfonates undergo C—O cleavage in preference to S—O cleavage and thus behave as alkylating agents. Similar remarks apply to the preparation of hydrazides of phosphorus



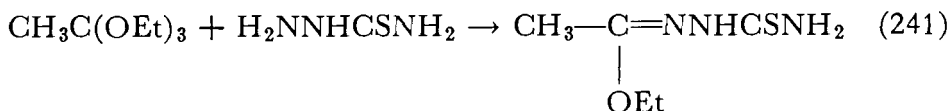
acids.⁷⁷ N'-Aryl arenesulfonylhydrazides are also available from the reaction of diazonium compounds with sulfur dioxide ²⁷³ (Eq. 240). Thionyl hydrazines are prepared by the action of thionyl chloride on



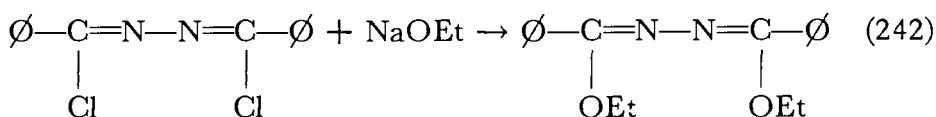
hydrazines containing an unsubstituted amino group.^{260, 274}

The preparation of hydrazonoyl halides may be accomplished either by the halogenation of aldehyde hydrazones (or azines),¹⁷³⁻¹⁷⁵ or by the action of phosphorus pentachloride on hydrazides,²⁴¹ as has been discussed in earlier parts of this chapter. Some alkyl hydrazonates have

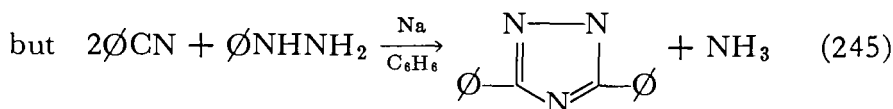
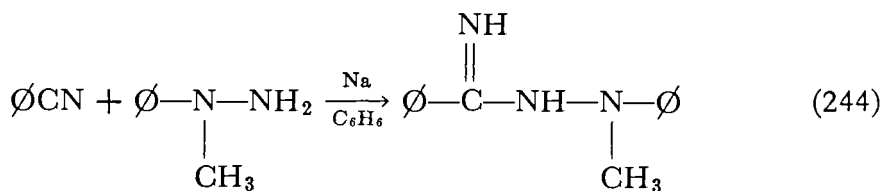
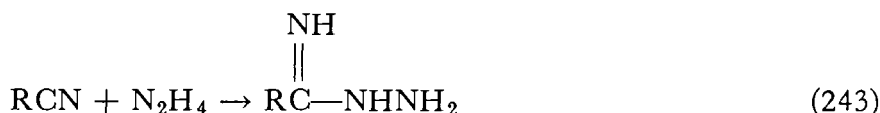
been made by the action of ortho esters on certain hydrazine derivatives ²⁷⁵ (Eq. 241). The displacement of chloride by ethoxide from a hydrazonoyl



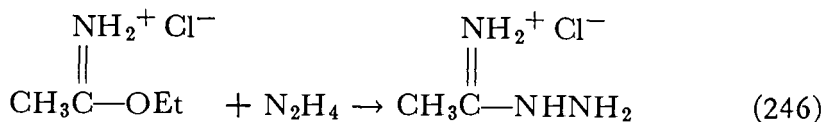
chloride has produced a hydrazone ester in one instance ^{253a} (Eq. 242) and may be a general reaction when there is no hydrogen on nitrogen. Direct alkylation of a hydrazide has led to a hydrazone ester in poor yield, in one example only. ^{231c}



AMIDRAZONES The most direct synthesis of amidrazones is the addition of hydrazines to nitriles ^{30a} (Eq. 243). The addition is sometimes difficult, however, and requires catalysis by the sodium salt of the hydrazine, prepared *in situ* by reaction with metallic sodium ²⁷⁶ (Eq. 244). The latter conditions appear to be successful only with *unsym*-disubstituted hydrazines, for with phenylhydrazine, two moles of nitrile react, giving



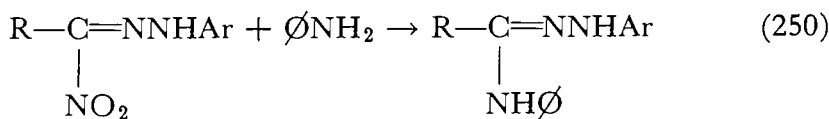
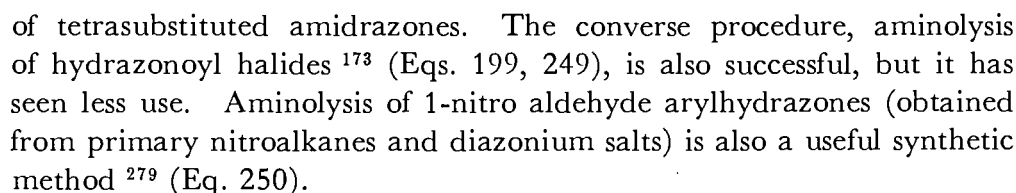
1,2,4-triazoles almost exclusively (Eq. 245). Closely related is the hydrazinolysis of imidate esters, ^{263, 277} which can, of course, be prepared readily from most nitriles, and which react more readily (Eq. 246).



$$\begin{array}{c} \text{O} \\ \text{O} \end{array} \text{—C=N—O} + \text{O—NHNH}_2 \rightarrow \begin{array}{c} \text{N—O} \\ \parallel \\ \text{O—C—NHNH—O} \end{array} \text{ and } \begin{array}{c} \text{N—O} \\ \parallel \\ \text{O—C—N—NH}_2 \\ | \\ \text{O} \end{array}$$

ratio 4:1

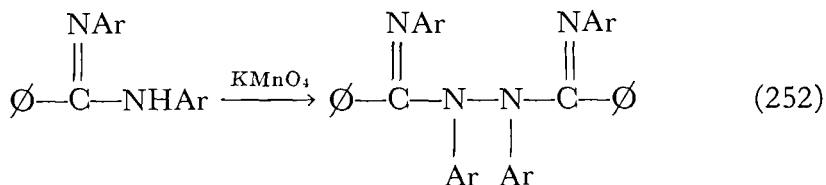
(247)


$$\begin{array}{ccc}
 \begin{array}{c} \text{N}-\text{N}-\text{Ar} \\ | \\ \text{R}-\text{C}^+ \\ | \\ \text{N}-\text{N}-\text{Ar} \end{array} & \xrightarrow{\text{Na}_2\text{S}_2\text{O}_4} & \begin{array}{c} \text{N}-\text{NHAr} \\ // \\ \text{R}-\text{C} \\ \backslash \\ \text{NH}_2 \end{array} \\
 \begin{array}{c} \text{N}-\text{NHAr} \\ // \\ \text{R}-\text{C} \\ \backslash \\ \text{NO}_2 \end{array} & \xrightarrow{\text{H}_2/\text{Pd}} & \begin{array}{c} \text{N}-\text{NHAr} \\ // \\ \text{R}-\text{C} \\ \backslash \\ \text{NH}_2 \end{array}
 \end{array} \quad (251)$$

of the arylhydrazones of 1-nitro aldehydes.^{216, 263} Reduction of tetrazolium salts,^{216, 263} which presumably passes through the hydrazidine

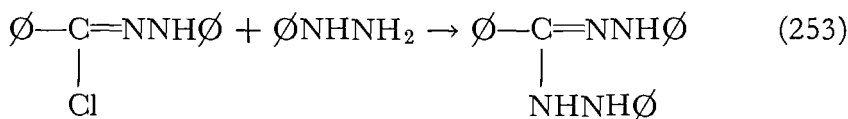
stage, also leads to the same class of amidrazones. Reduction has also been used to prepare some formamidrazones, through desulfurization of thiosemicarbazides.²⁵³

Some N,N-*bis*-amidrazones have been prepared by the oxidation of N,N-diaryl amidines²⁸⁰ (Eq. 252).

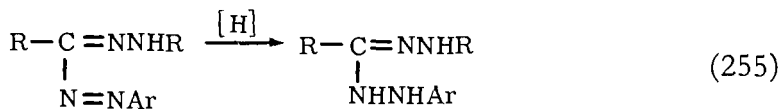
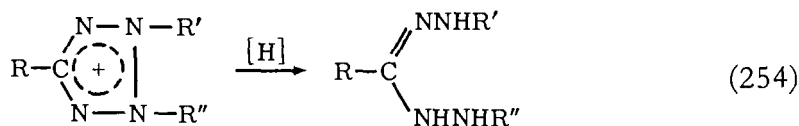


Semicarbazides, as their structure is ordinarily written, are tautomers of the amidrazone structure, and their synthesis should be mentioned here. There are many methods, most of which are solvolytic, some reductive, and so numerous that a special review²⁷⁰ has been devoted to them.

HYDRAZIDINES The preparation of hydrazidines by hydrazinolysis reactions appears to be confined to the use of hydrazonoyl chlorides^{241a, 281} (Eq. 253), although other ways should be feasible. Another fairly general

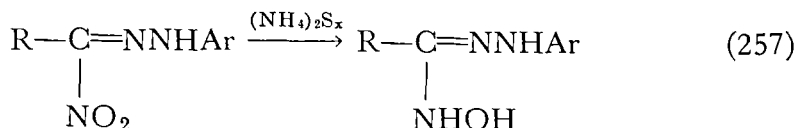
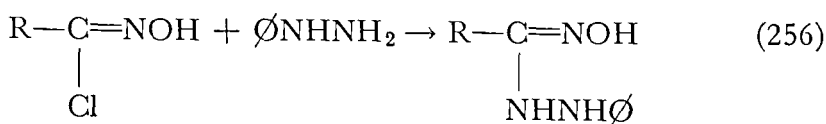


route, leading to hydrazidines disubstituted with alkyl or aryl groups, is the careful reduction of tetrazolium salts^{216, 263} or of formazans²⁸² (derived from diazonium salts and aldehyde hydrazones) (Eqs. 254, 255).



Hydrazidines bearing carboethoxy groups on nitrogen have been obtained by the reaction of aldehyde hydrazones with azodicarboxylic ester.¹⁸⁹

Hydroximoyl hydrazines (or hydrazonoyl hydroxylamines) are prepared by the hydrazinolysis of hydroximoyl halides,²⁸³ or by the partial reduction of 1-nitro aldehyde hydrazones²⁸⁴ (Eqs. 256, 257).



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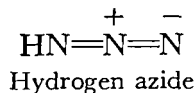
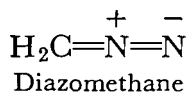
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chapter | Azides and Diazo ten | Compounds

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Diazomethane and hydrogen azide, the parents of diazo compounds and azides, are isoelectronic and show much similarity, in themselves and in their derivatives. Both are volatile, unstable substances, rich in energy to the point of explosiveness, and both show a large variety of reactions resulting either from loss of nitrogen or 1,3-addition. It is convenient, therefore, to treat them together in the same chapter; nitrile imines are also included, since they are isomeric and sometimes even tautomeric with diazoalkanes.



NOMENCLATURE

Azides are named in the same way as halides, with the name of the substituent radical followed by the separate word "azide," or with the prefix "azido." The former method is used whenever feasible, for the azido group is generally the most important part of the molecule and

takes the emphasis: $\text{C}_6\text{H}_5\text{N}_3$, phenyl azide (azidobenzene); CH_3CON_3 , acetyl azide. The older terms "azoimide," "azimido," and "triazos" are found widely used in the older literature, but have been in disuse for a long time.

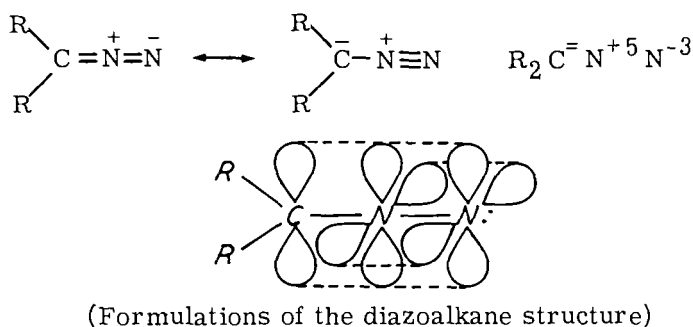
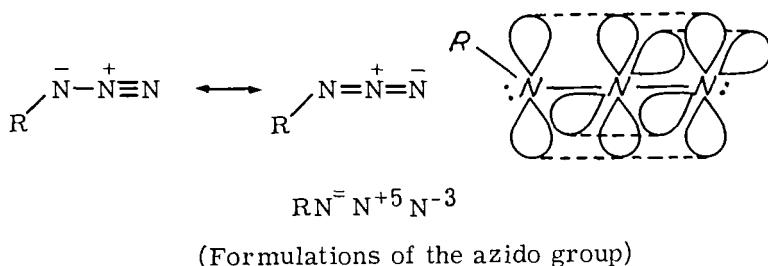
Diazo compounds are usually named by use of the prefix "diazo," which stands for the divalent radical $\text{N}_2=$, but sometimes for convenience or emphasis they are named as substituted diazomethanes: $\text{CH}_3\text{COCH}=\text{N}_2$, diazoacetone; $\text{C}_6\text{H}_5\text{CH}=\text{N}_2$, phenyldiazomethane.

Azides are not found in nature, but the antibiotic azaserine,¹ $\text{N}_2\text{-CHCOOCH}_2\text{CH}(\text{NH}_2)\text{COOH}$, isolated from *Streptomyces* cultures in 1954, is an example of a naturally occurring diazo compound.

PROPERTIES ²

Hydrogen azide is a colorless liquid that boils at 35° , but it is not really representative of alkyl azides, owing to its acidic hydrogen. Methyl azide has a lower boiling point, $20\text{--}21^\circ$, showing that there must be appreciable hydrogen bonding in the parent compound. Diazomethane is an orange gas, bp -23° , mp -145° , and diazoethane boils at $-18^\circ/89.5$ mm. These boiling points are high for substances of low molecular weight without hydrogen bonding (compare propene, bp -48° and butene-1, bp -5°), and must therefore be a consequence of an appreciable dipole moment (that of diphenyldiazomethane is 1.42 D^3). Vinyl azide is a clear yellow liquid, bp $28\text{--}30^\circ$, dipole moment 1.12 D^4 . The only reported N-azido compound, $(\text{CH}_3)_2\text{N}-\text{N}_3$, is an explosive liquid, bp $32^\circ/11\text{ mm}^5$. The dipole moments of phenyl azide (1.55 D) and *p*-chlorophenyl azide (0.33 D) show that the azido group is markedly negative with respect to carbon.

The structure of both the azido and the diazomethyl groups is now known to be linear, although both groups were for a long time written as three-membered rings, which represented the only possibility in terms of classical Kekulé theory and trivalent nitrogen. X-ray and electron diffraction patterns ⁶ indicate a linear structure, with substituents on the azide nitrogen or diazomethane carbon lying at an angle of about 120° . Although the azide ion is completely symmetrical, in organic azides the unsubstituted nitrogens are slightly closer together. These facts are represented by structural formulas in three different ways: resonance hybrid, delocalized molecular orbital, and as a coordination structure isoelectronic with nitrate. On the basis of the last formulation, Franklin ⁷ referred to hydrogen azide as "ammononitric acid," since $\text{HO}^- + 2\text{O}^-$ are equivalent electrically to $\text{HN}^- + \text{N}^{-3}$.



The infrared spectra of both azides ^{8a} (2140–2240 cm.⁻¹, often a doublet) and diazo compounds (2040–2120 cm.⁻¹) ^{9a} show absorption in the range where the stretching frequencies of triple bonds and allenic systems are usually found. The azido group absorbs very weakly in the near ultraviolet, ^{8b} but never in the visible range; alkyl, aryl, and acyl azides are thus colorless. Alkyl azides generally show a band near 2870 Å, $\epsilon \simeq 25$, attributed to a $\pi \rightarrow \pi^*$ transition, and a stronger band near 2160 Å. Diazo compounds are generally intensely colored in the range from canary yellow to garnet red.

The NMR signal of the hydrogens of diazomethane has been observed ^{9b} at $\tau = 6.92$; anisotropic deshielding by the C=N bond is evidently much weaker than that by carbonyl or ethylenic double bonds.

It is interesting that an isomer of diazomethane having the diaziridine ring structure was actually isolated ¹⁰ in 1961; it is a colorless gas, bp -14° , and is less reactive than diazomethane. A tautomer of diazomethane,

$\text{HC}^--\text{N}^+=\text{NH} \leftrightarrow \text{HC}\equiv\text{N}^+-\text{NH}^-$, called "isodiazomethane" (or formonitrile imine), is also known ^{11a}; it is an almost colorless oil that decomposes at room temperature and explodes at $35-40^\circ$. The correct assignment of structures to these systems derives strong support from experiments with isotope labeling with ¹⁵N, by means of which the complete equivalence of the two diaziridine ^{10b} nitrogens and the nonequivalence of the two diazoalkane ^{11b} nitrogens has been demonstrated.

Neither azides nor diazoalkanes are basic in the sense of being able

to form salts with acids, but they are capable of accepting protons, as shown by their sensitivity to acid-catalyzed decomposition. The value of -6.21 for pK_a for $H_2N_3^+$ has been estimated,¹² an extremely low basicity indeed; the van't Hoff i -factor of sodium azide in concentrated sulfuric acid, ~ 4 , indicates complete protonation to $H_2N_3^+$.¹³ Diazo compounds are much more sensitive to acids, and are presumably stronger bases.

Azides and diazo compounds are traditionally thought of as explosive, because of the properties of the parent compounds. The heat of formation of the azido group is 205–208 kcal/mole, and that of the diazoalkane group is similarly high, showing that a great deal of energy can be released when such compounds decompose. The maximum energy is released only when molecular nitrogen, N_2 , is formed. When the carbon-containing part of the molecule is sufficiently large, however, these compounds lose their explosive characteristics, since the energy released on decomposition is then distributed over a large "dead weight" of carbon. It cannot be said precisely where explosiveness ends, but it is probably not far from a ratio of $(C + O)/N = 3/1$. Sensitivity is not just a function of size, however, and although methyl azide can be handled in an almost routine manner (but not in the presence of mercury¹⁴), acetyl azide is treacherously explosive. It is therefore advisable to handle all azides and diazo compounds with caution and protection against the eventuality of explosion, until experience has shown the characteristics of the particular example at hand.

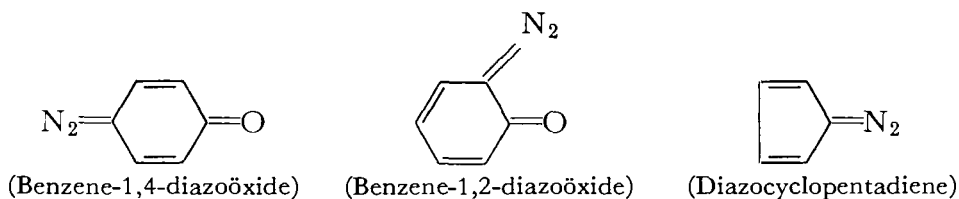
The electronic properties of the azido group have been determined from its effect on the strengths of acids and bases to which it is attached and on the reactivity of the benzene ring.¹⁵ It has an electron-withdrawing inductive effect, which is counteracted in *ortho*- and *para*-substituted benzene compounds by a mesomeric effect. For example, *m*-azidoaniline is a weaker base than aniline or its *para* isomer, and phenyl azide is more easily attacked (*para*) than benzene.

Hydrogen azide, which is used as a reagent in organic chemistry, is quite safe in dilute solution, but is violently explosive and treacherously sensitive in the concentrated or pure state. For this reason it is advisable to add some ether or pentane to its solutions, since these solvents, having similar boiling points to hydrogen azide, prevent its inadvertent concentration by evaporation and recondensation. Pure hydrogen azide has often been isolated by distillation, but appears to undergo rapid sensitization on standing, such that within an hour, faint vibrations or perhaps even voices can detonate it. Diazomethane, even in solution, shows a similar aging phenomenon, and it is a most dangerous practice to store diazomethane solutions, even at refrigerator temperatures.

Diazomethane is extremely poisonous, and its inhalation should be

carefully avoided. Some chemists become sensitized to it after the first exposure, after which even scarcely detectable traces of the substance put them in acute misery. Hydrogen azide is much less toxic, but it does have an unpleasant vasodilating effect. Exposure to its vapors congests the nose, makes the eyes bloodshot, and flushes the face, making the ears red and hot. Fortunately, these conditions disappear after a few minutes in fresh air, and there appear to be no aftereffects. (Swallowing a small volume of undiluted alcohol, once recommended as an antidote, is of unsubstantiated worth.)

In addition to the ordinary, unconjugated diazo compounds that are ordinarily brought to mind by the term "diazoalkane," there are conjugated diazo compounds that have about as much in common with diazonium salts as with diazoalkanes. These are the "diazo oxides" and diazocyclopentadiene. Benzene-1,4-diazooxide,¹⁶ also known less appropriately as "*p*-quinone diazide," is an orange solid that explodes at 92° and shows infrared absorption at 2080 cm.⁻¹ typical of diazo compounds.

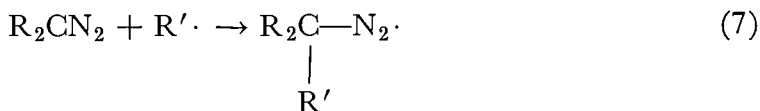
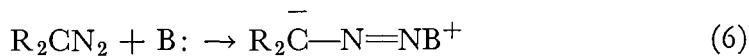
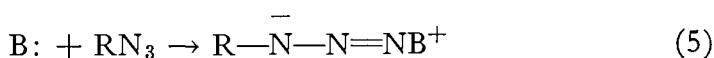
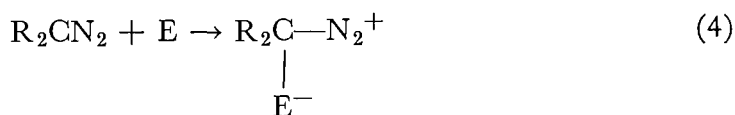
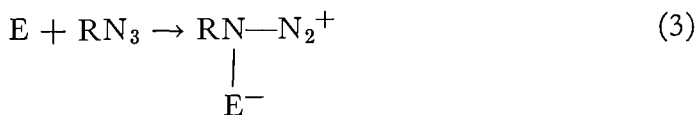


Diazocyclopentadiene¹⁷ is an unusually stable oil, bp 45°/40 mm., and readily undergoes typical aromatic electrophilic substitution reactions at the 2- and 5-positions. The chemistry of these classes of compounds is discussed in this chapter only insofar as it resembles that of other diazo compounds; that part of their chemistry that is of typically diazonium nature is taken up in Chapter 11.

REACTIONS ²

It is convenient to classify the reactions of azides and diazo compounds according to the initial steps, which may be: (1) cleavage into nitrogen and an electron-deficient species, RN or R₂C (Eqs. 1, 2); (2) attack by an electrophilic atom, at the substituted nitrogen of azides or the carbon of diazo compounds (Eqs. 3, 4); (3) attack by a nucleophilic atom, at the terminal nitrogen (Eqs. 5, 6); (4) reactions with free radicals (Eq. 7). The initial products of such steps are in nearly all cases reactive intermediates that cannot themselves be isolated; the final products result from one or more additional steps, of which there are many possibilities, leading to a wide variety of end products. In a few cases the same type of end

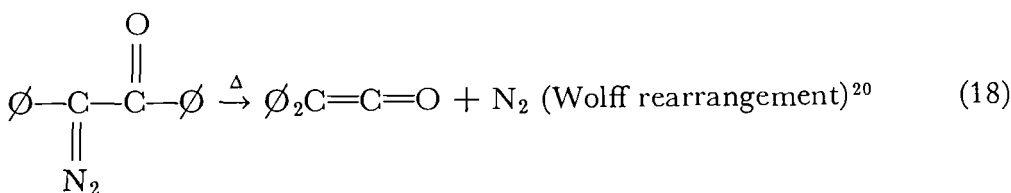
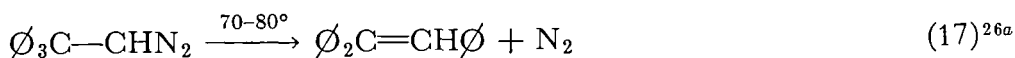
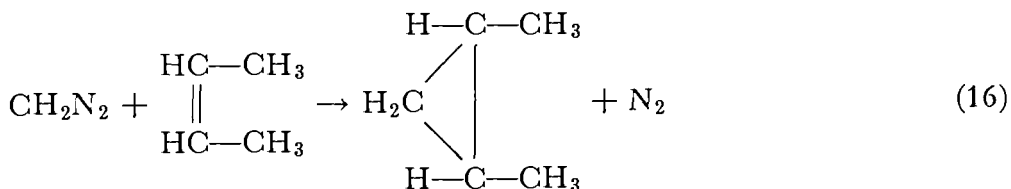
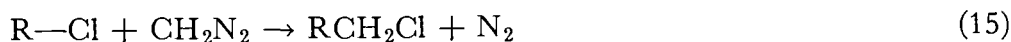
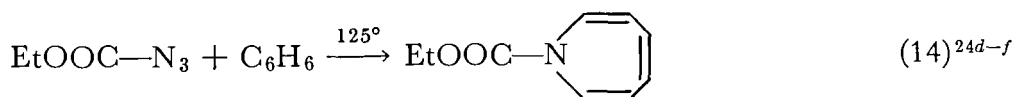
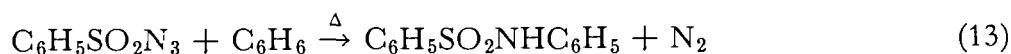
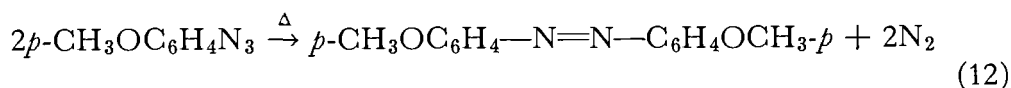
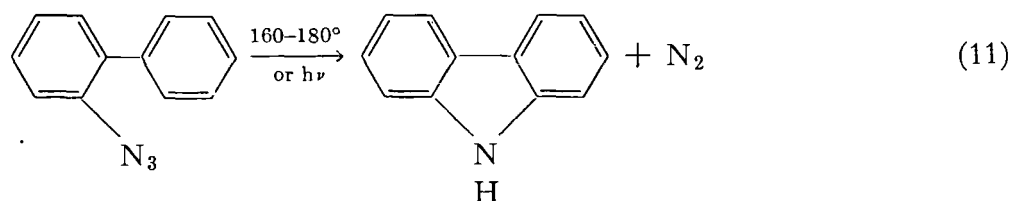
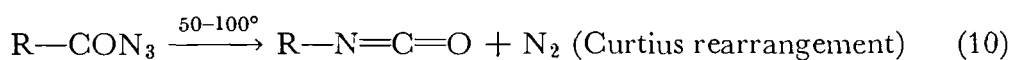
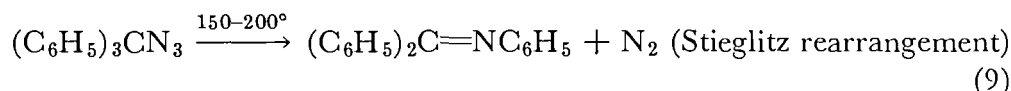
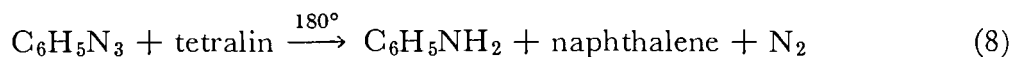
product can be obtained through different initial steps, so the structure of the end product is not by itself sufficient indication of the path by which it was formed.

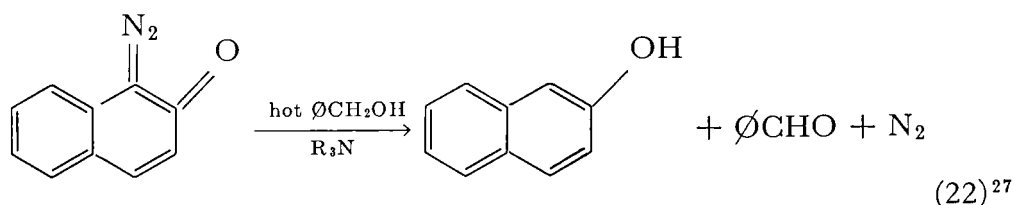
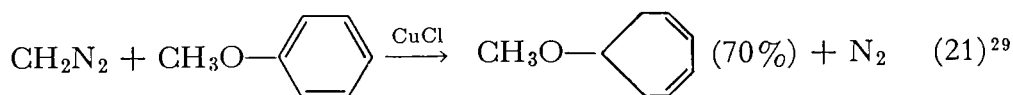
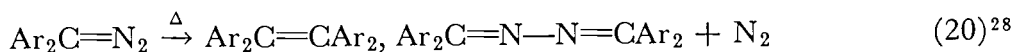
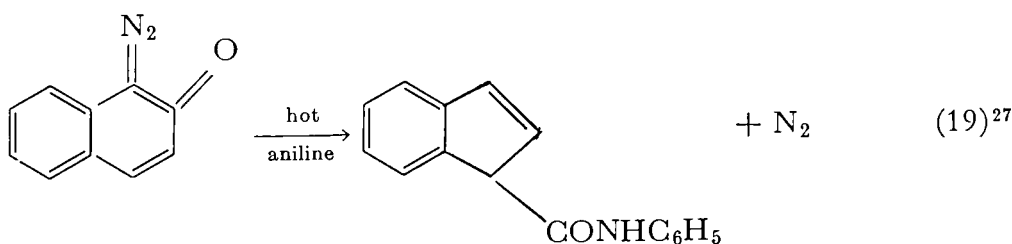


FRAGMENTATION Azides and diazo compounds readily lose two atoms of nitrogen when they are heated or exposed to ultraviolet light (Eqs. 1, 2) (or certain catalysts—usually copper—in the case of diazo compounds). Such decomposition need not be explosive and can always be controlled by dilution with an inert solvent. An array of evidence indicates that the first step is the separation of a molecule of N_2 and the formation of an electron-deficient fragment, a diradical, very short lived at ordinary temperatures. These species are derivatives of methylene ¹⁸ (or carbene), CH_2 , or of NH ^{18a,19} (variously called azene, imine, nitrene, imene, azylene, imidogen, etc.), which may have their unshared electrons paired or unpaired (i.e., CH_2 : or $\cdot\text{CH}_2\cdot$), depending on the substituents and the conditions of formation. (In some cases the loss of nitrogen may be accompanied by a simultaneous rearrangement or followed by one so rapidly that these intermediates are not really free and cannot be detected by other chemical reactions.²⁰) It has been suggested that some of the reactions attributed to carbenes derived from photolysis of diazo compounds are actually those of a photoexcited diazo compound,²¹ however.

THERMOLYSIS AND PHOTOLYSIS The substances eventually formed by such decompositions vary widely with structure, with the nature of other substances that may be present, and with the conditions, and are nearly always interesting. The commonest reactions with azides (Eqs. 8-14)

are ²²: hydrogen abstraction, forming a primary amine ^{22a}; rearrangement to products with N—C double bonds ^{20, 22b-d}; cyclization ^{22a, 23}; dimerization to an azo compound ^{22a}; and addition to a C—H or C=C bond of another molecule.²⁴ Diazo compounds show the same reactions (Eqs. 15–22), but their relative importance is different, addition ²⁵ to C=C and C—H being much favored over hydrogen abstraction, and rearrangement ²⁶ (1,2 shift) being less common.



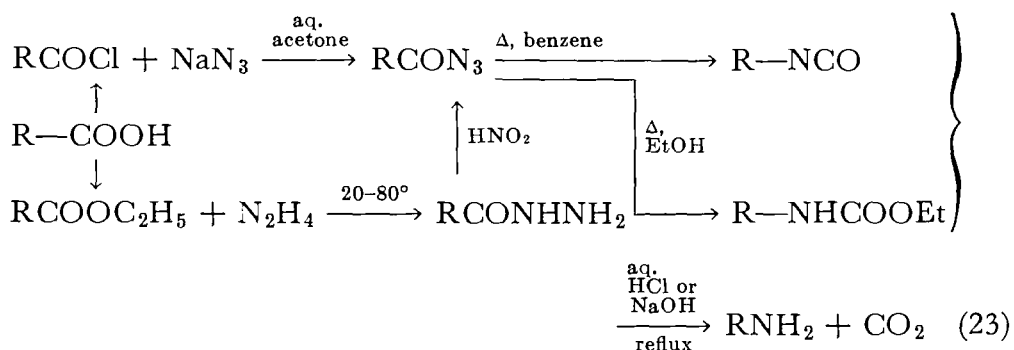


A considerable amount of evidence is available^{18c, 25} that methylene radicals are produced in most cases initially in the singlet state (electrons paired, $\text{CH}_2:$), which is an excited state, more reactive and of higher energy than the triplet state (electrons not paired, $\text{CH}_2\cdot$). They may be converted by collisions to a more stable triplet state if they do not react in some way beforehand. The reactions of the two states are slightly different; for example, the singlet state adds stereospecifically to *cis*-butene-2, giving *cis*-dimethylcyclopropane, but the triplet state gives a mixture of *cis* and *trans* product. The picture is not unambiguous, however, for carbenes generated in different ways may show marked differences in selectivity, which may be the result of association with other reagents present (e.g., lithium bromide).^{25c} The information is less complete on the nature of the intermediates from azides, but most of the evidence favors a triplet state for the intermediate $\text{R}-\text{N}$ as formed from simple azides.^{21, 30}

Of the foregoing types of reactions, the most important from a practical standpoint are the rearrangements of the acyl derivatives: the Curtius and Wolff rearrangements. The Curtius rearrangement^{20, 31} is the key step in a widely used method for converting a carboxylic acid to an amine of one less carbon atom; the Wolff rearrangement²⁰ is the key step in the Arndt-Eistert synthesis,³² whereby a carboxylic acid is converted to its next higher homolog. Only simple acyl azides and α -diazo ketones appear to be generally capable of such rearrangements; sulfonyl, carbamyl, and alkoxycarbonyl azides have been observed to give rearrangement products only as a result of photolysis in methanol,^{31b} a fact that suggests

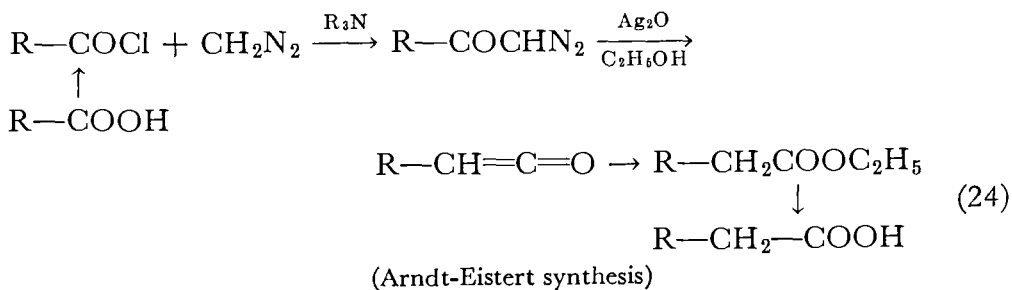
that a species hydrogen-bonded with the solvent does the actual rearranging in such cases

CURTIUS REARRANGEMENT In the Curtius degradation, an acyl azide is prepared either by reaction of an acyl chloride with sodium azide, or of a hydrazide with nitrous acid. The acyl azide more often than not is not isolated, but is warmed in an inert solvent to convert it to an isocyanate, or in alcohol to convert it to a urethan (Eq. 23). If an amine is the ultimately desired product, then the initial rearrangement products must be hydrolyzed; refluxing with hydrochloric acid or aqueous alkali is usually quick and effective. The overall yields are usually good, and the conditions can be kept quite mild.

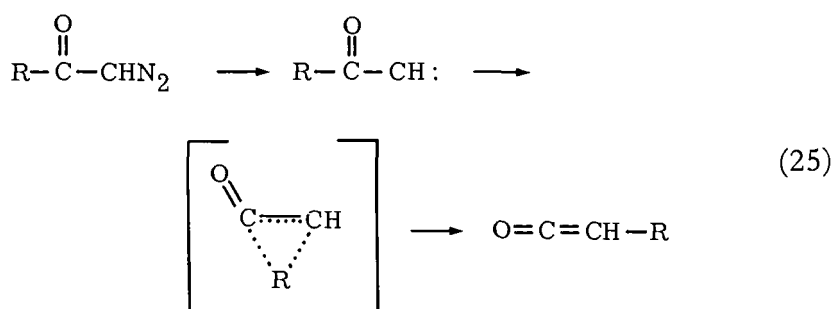


(Curtius degradation of an acid through its azide)

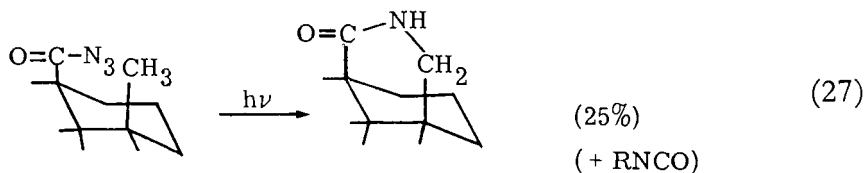
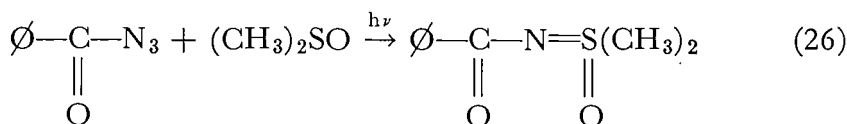
ARNDT-EISSERT SYNTHESIS In the Arndt-Eistert synthesis, an acid chloride reacts with diazomethane (or a higher diazoalkane) to give an α -diazo ketone (an acyl diazomethane), which is usually best rearranged by heating, usually with a silver-containing catalyst, in the presence of a substance such as ammonia or alcohol that will combine with the ketene first formed (Eq. 24). When a substituted diazomethane is used, an α -substituted acid derivative is produced.³³ Experiments with isotopic carbon have shown that the carbon atom of the carboxyl group of the product is the same one that was in the carboxyl group of the starting acid.³⁴ The biggest application of the synthesis is with diazomethane; although interesting α -substituted acids can be made by this synthesis, practical difficulties somewhat limit its application with higher diazoalkanes.



CURTIUS AND WOLFF REARRANGEMENTS; MECHANISM The Curtius and Wolff rearrangements both involve a migration of a group from a carbonyl group to a neighboring atom, a process sometimes called a 1,2-shift. It has been demonstrated in many ways that this migration is strictly intramolecular; the migrating group never gets free of the system to which it is attached at the start and finish, and attempts to intercept it in the form of an ion or radical have all failed. When optically active compounds are used in which the carbonyl group is attached directly to the site of optical activity, the products are found to have been formed with full retention of activity and configuration.³⁵ It is clear, therefore, that the bond to the migration terminus (C or N) is being formed at the same time as the original bond to the carbonyl group is being broken (Eq. 25).

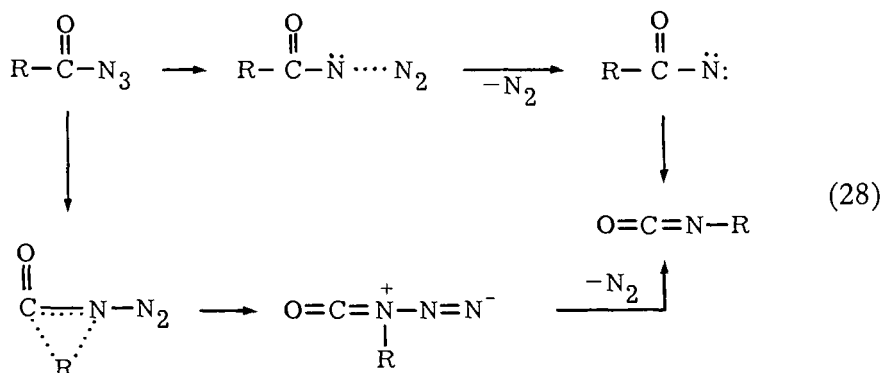


The rearrangements of the presumed electron-deficient intermediates are so fast that it has been possible to intercept them in Curtius rearrangements only in two cases^{24c, 36} (Eqs. 26, 27) of photo-induced rearrangement and only in a few case of the Wolff rearrangement.^{27, 37} However,

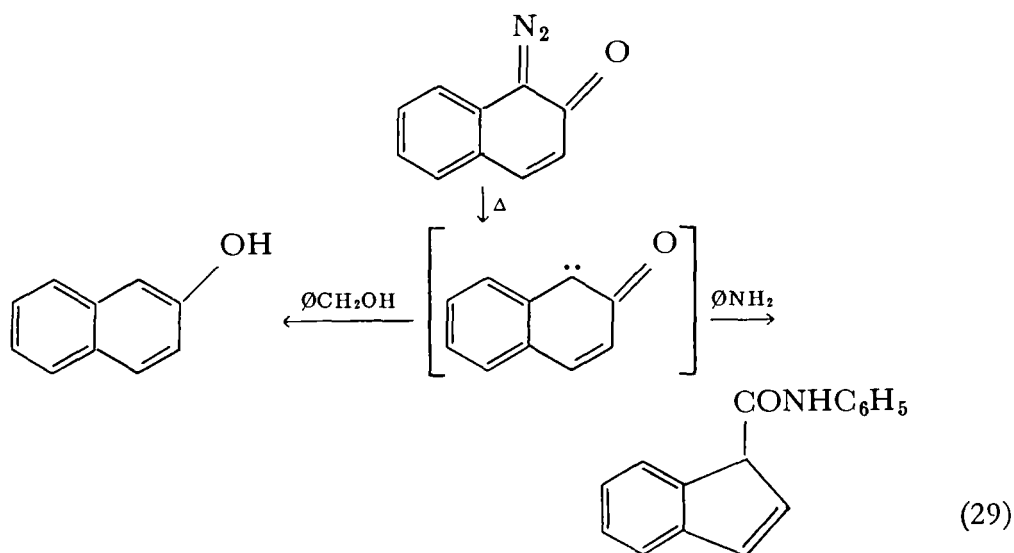


when acyl azides that do not readily undergo Curtius rearrangement, such as ROCON_3 ^{24, 38} and ArSO_2N_3 ,²⁴ are caused to lose nitrogen by exposure to heat or light, reactions convincingly attributable to $\text{ROCO}-\text{N}$ or ArSO_2-N are observed. This alone is not sufficient evidence to conclude that Curtius rearrangement also proceeds through such intermediates, although it may, for it would be reasonable to expect that the migration of R from C to N could in favorable cases be concerted with breaking of the N—N bond. There may, indeed, be a nearly continuous

spectrum of transition states between the extremes represented by complete loss of nitrogen before migration and completed migration before loss of nitrogen (Eq. 28). There is no reason to believe that the transition states are identical for all cases of the Curtius rearrangement (or for all cases of the Wolff rearrangement).

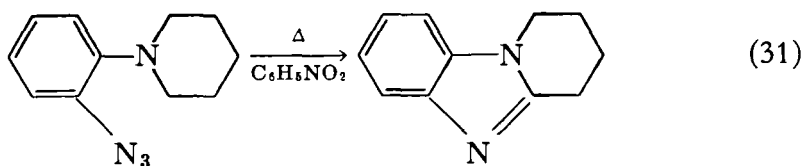
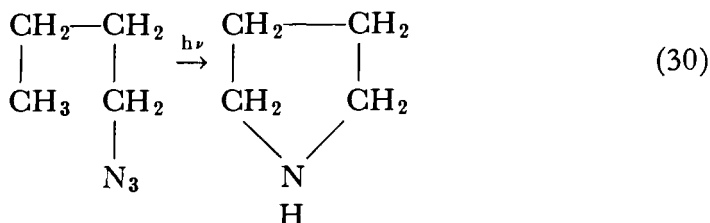


There is better evidence that loss of nitrogen may be completed before migration in some Wolff rearrangements, for carbene intermediates have apparently been intercepted.^{27, 37} For example, naphthalene-1,2-diazo-oxide rearranges at about 180° in the presence of aniline, but in the presence of benzyl alcohol and an amine at the same temperatures, reduction takes place to give β -naphthol²⁷ (Eq. 29).



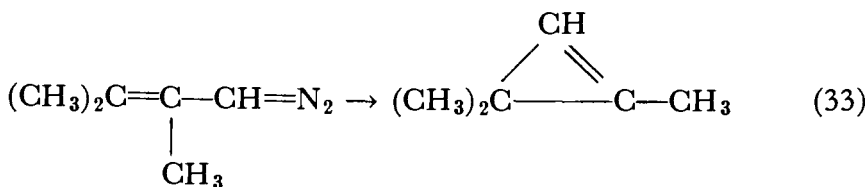
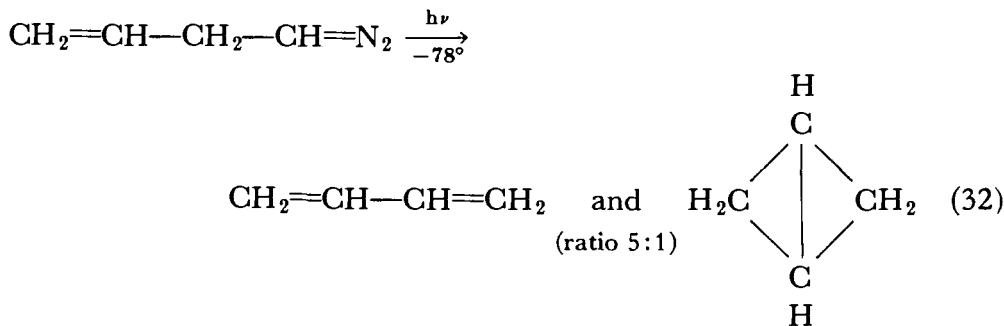
OTHER REACTIONS OF $\text{R}-\ddot{\text{N}}:$ AND $\text{R}_2\text{C}:$ The other reactions that proceed through formation of an electron-deficient radical are generally of less importance to a large extent because so many of them lead to mixtures of products with low yields. The cyclization reactions of azides^{21, 23} are an exception, and many 5-membered heterocyclic compounds can

be made in good yields (Eqs. 30, 31) (rings of other sizes can also be formed, but the reactions are not as general or as smooth). The reactions

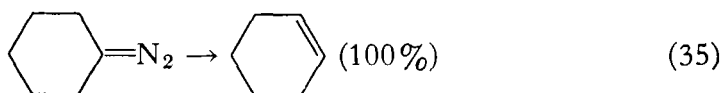
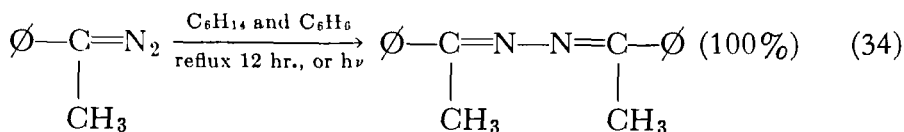


of diazo compounds with benzene rings,²⁹ which lead to cycloheptatrienes, are often used in spite of the fact that the yields may be low, because other synthetic routes are usually laborious and give even lower overall yields; cuprous chloride catalysis considerably improves the yield, however.²⁹ These reactions, as exemplified by that of diazoacetic ester with benzene (Eq. 14), were for a long time believed to occur by initial addition to form a cyclopropanocyclohexadiene (norcaradiene), which subsequently isomerized. Although this may indeed be the case, it was eventually demonstrated by nuclear magnetic resonance that the supposed norcaradiene derivatives were in fact isomeric cycloheptatrienes.^{18c, 29b}

The carbenoid addition of diazoalkanes to olefins has assumed importance as a preparative method for cyclopropanes; it can be applied intramolecularly to unsaturated diazoalkanes to produce unusual cyclic structures, such as bicyclobutane and cyclopropenes^{25e} (Eqs. 32, 33).



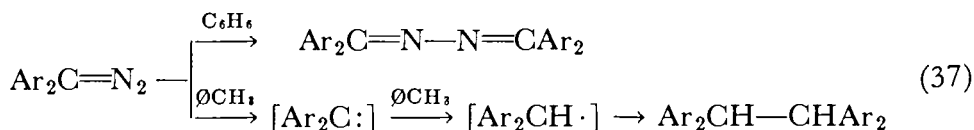
The formation of azines from diazoalkanes (Eq. 20) deserves special mention, for it is a competing reaction in many processes, and its mechanism has been a subject of active discussion. Purely thermal decomposition of diazoalkanes nearly always produces traces of azine; the amount may be quite substantial with aryl diazomethanes,^{28b} but is often negligible with aliphatic compounds, which give hydrocarbons instead (e.g., Eqs. 34 and 35).



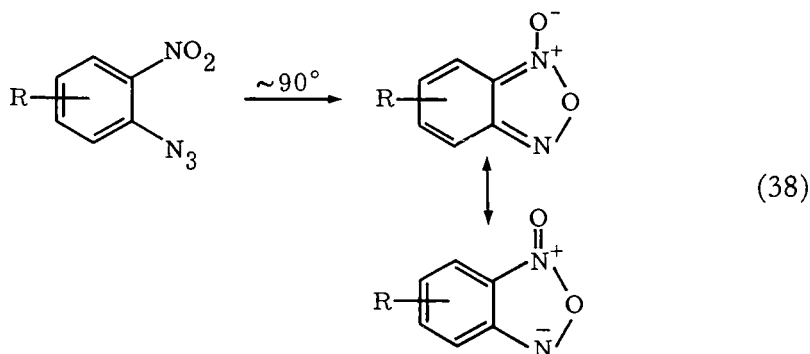
The fact that 1-phenyldiazoethane forms acetophenone azine as nearly the sole product, whereas the isomeric diaziridine forms styrene,^{28c} has been interpreted as evidence that the azine is not formed by combination of a carbene with an undecomposed molecule of diazoalkane, but results from dimerization before nitrogen is lost. Such dimerization can be formulated as electrophilic attack by the terminal nitrogen of one molecule on the α -carbon of another ^{28d} (Eq. 36). On the other hand, the

rate of evolution of nitrogen from diphenyldiazomethane has been found to be first order,^{28a} which is consistent with the carbene route, but not with the prior dimerization route. An alternative route involving catalysis of dimerization by bases has also been proposed ^{28a}; an instance of acid-catalyzed azine formation is described further on. A competing factor in thermal decomposition of diazoalkanes is the fact that azines themselves decompose if the temperature is high enough; furthermore, azine decomposition is catalyzed by diazoalkane (see Chapter 9). As a result, conversion to azine is likely to be higher when the decomposition of the diazoalkane is conducted at a minimal temperature. Another factor affecting azine formation is the ability of the medium to act as a

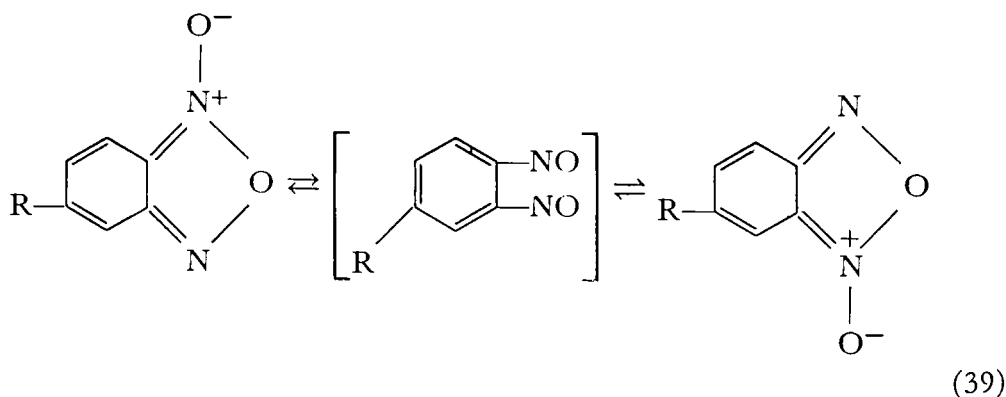
source of hydrogen; hydrogen abstraction by an intermediate carbene is presumed to be responsible. The higher conversion to azine is observed in such solvents as benzene; in solvents that are better hydrogen-donors, such as toluene, saturated hydrocarbons are favored (Eq. 37).



o-Nitroaryl azides undergo a type of cyclization different from those just considered, in that bonds to hydrogen are in no way involved. Nitrogen is lost at much lower temperatures than with other aryl azides, and a benzofuroxan is formed by attack on an oxygen atom (Eq. 38).³⁹ The kinetic features of the reaction also suggest that the reaction is different from those of other aryl azides and is a concerted process, in which the new N—O bond is being formed at the same time as N₂ is being released. The structure of the products has been controversial, for a 4-substituted 2-nitrophenyl azide gives the same benzofuroxan as the 5-substituted



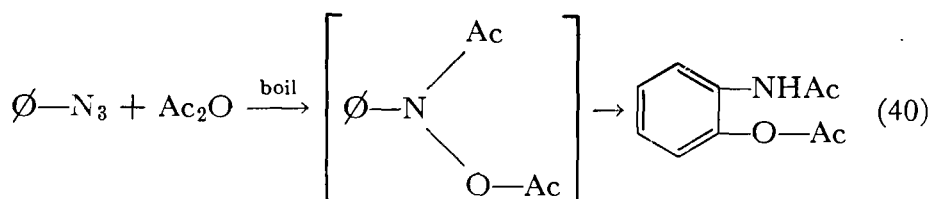
azide. Nuclear magnetic resonance spectra indicate,^{39c} however, that there is rapid interconversion among pairs of isomeric benzofuroxans, perhaps through brief ring opening to an *o*-dinitroso compound (Eq. 39).



Cyanogen azide undergoes fragmentation without catalysis at unusually low temperatures (40–60°). The reactive intermediate, NCN, is

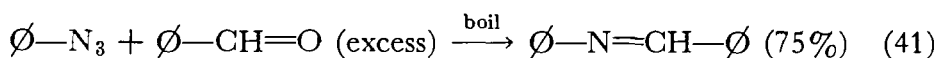
symmetrical in its reactivity, and expands benzene rings and inserts in C—H bonds of alkanes with high efficiency.⁴⁰

Two further thermal reactions of azides deserve comment.⁴¹ Decomposition of phenyl azide in boiling acetic anhydride gives *o*-acetoxyacetanilide, probably through an isomeric phenylhydroxylamine derivative (Eq. 40) (cf. Chapter 8). Decomposition in boiling cyclohexanone

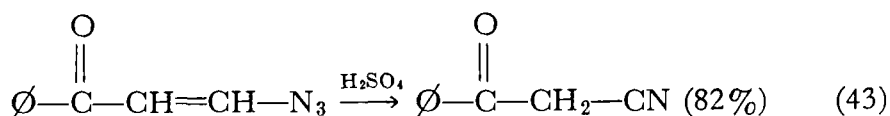
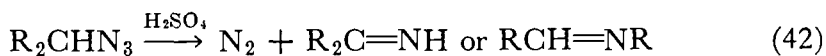


or benzaldehyde gives the corresponding anils (Eq. 41). This type of reaction perhaps goes through an oxaziridine, followed by reduction by

excess carbonyl compound; the nitrones, such as $\text{C}_6\text{H}_5\text{CH}=\text{N}^+\text{C}_6\text{H}_5\text{O}^-$, are stable under the conditions.

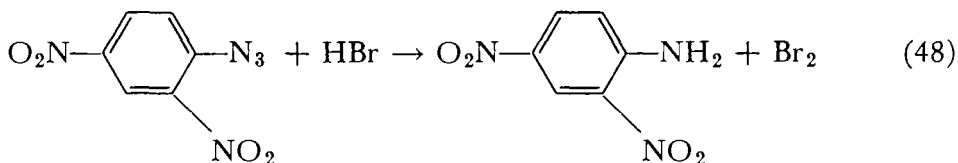
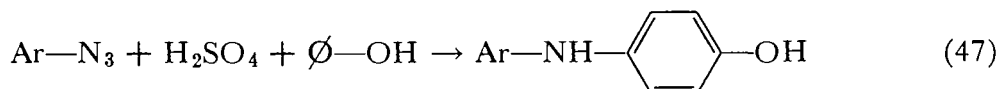
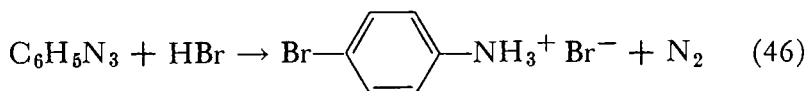
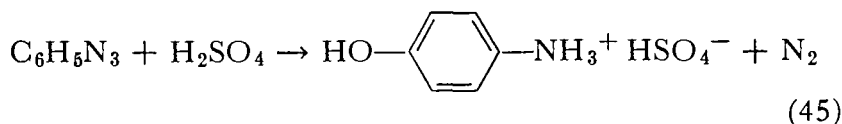
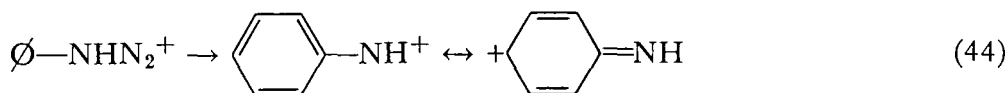


AZIDES AND ACIDS The reactions with Brønsted acids (sources of H^+) are the most important of the reactions of azides and diazo compounds with electrophiles. Azides are inert to dilute acids, but almost all of them react with concentrated sulfuric acid at room temperature with loss of nitrogen. Nitrogen evolution is usually quantitative and has even been used for quantitative analysis for the azide function.⁴² Aliphatic azides are usually rearranged by such treatment,²⁰ an α -substituent (hydrogen or alkyl) migrating to the retained nitrogen to form an aldimine or ketimine,^{43a} which in the case of vinyl azides isomerizes to nitriles^{43b} (Eqs. 42, 43). Aryl azides do not rearrange, but usually react with the anion



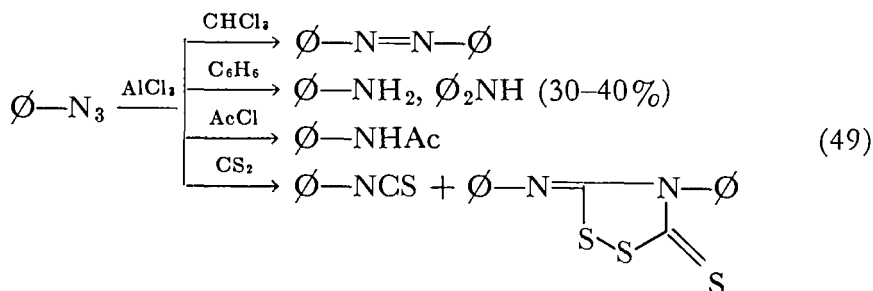
of the acid or with the solvent, forming ring-substituted anilines.⁴⁴ Azides that cyclize when heated or irradiated do not cyclize when decomposed with acid. Evidence is not yet sufficient to specify the paths of these reactions, but it appears that the conjugate acids of azides, Ar-NH-N_2^+ , are first formed, since the kinetics are roughly first order in ArN_3 and the acidity function h_0 .⁴⁵ Such species may undergo nucleophilic displacement at the substituted nitrogen atom, producing haloamide or hydroxylamine derivatives that then undergo rearrangement or other reactions, or they may lose nitrogen unimolecularly, producing a reactive delocal-

ized cation (Eq. 44), which may combine with a nucleophile in a subsequent step (Eqs. 45–47). Such species may be responsible for the intense colors that are formed in concentrated sulfuric acid, but are destroyed on dilution (compare aryl hydroxylamines, Chapter 8). *Para*-substituted aryl azides may be converted by strong mineral acids to *ortho*-halo or *ortho*-hydroxy anilines, to anilines without further substitution (Eq. 48), or to polymeric substances of the type $(R-C_6H_4-N)_x$.⁴⁶

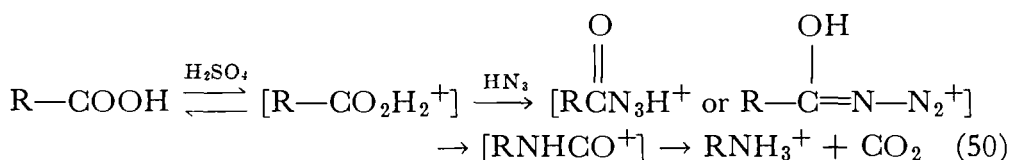


The overall behavior of aryl azides toward strong acid is very like that of the corresponding N-aryl hydroxylamines, except for the lack of azoxy compounds among the products, and it is possible to correlate the various reactions by the hypothesis that an anilino cation is a common intermediate (cf. Chapter 8).

Lewis acids, such as anhydrous aluminum chloride, also react with most azides. The products are somewhat different to those from Brønsted acids: phenyl azide, for example,⁴⁷ is converted to azobenzene or to aniline and diphenylamine, accompanied by much tar, or may react with solvent in suitable cases. In the absence of a diluent, explosion may occur.

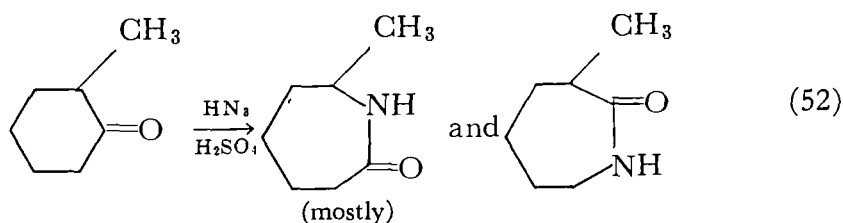
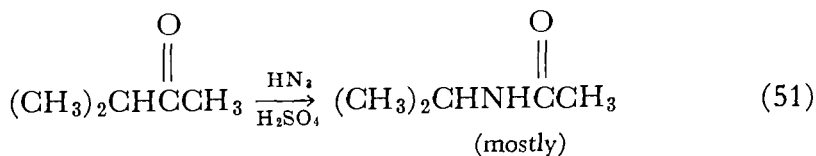


SCHMIDT REACTION WITH ACIDS Acyl azides undergo either solvolysis or rearrangement at room temperature when treated with strong acid; such catalysis is so effective that the reaction may be uncontrollably violent unless the diluted azide is brought into contact with the acid in small portions. The most useful application of this phenomenon is the generation of the protonated azide *in situ* by treatment of a carboxylic acid with excess hydrogen azide in the presence of concentrated sulfuric acid. This procedure is known as the Schmidt reaction^{20, 48} and constitutes a one-step conversion of a carboxyl group to an amino group (the isocyanate presumably formed first is usually rapidly hydrolyzed by the reaction medium) (Eq. 50). The Schmidt reaction is a fast and simple

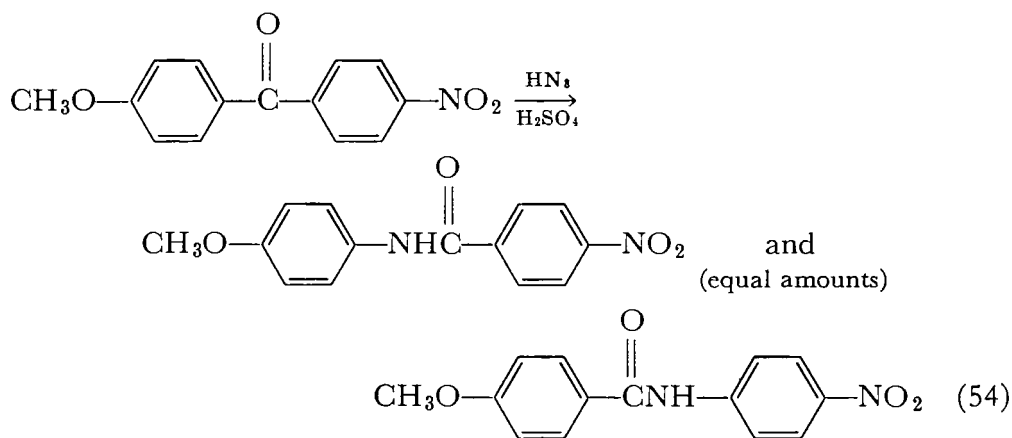
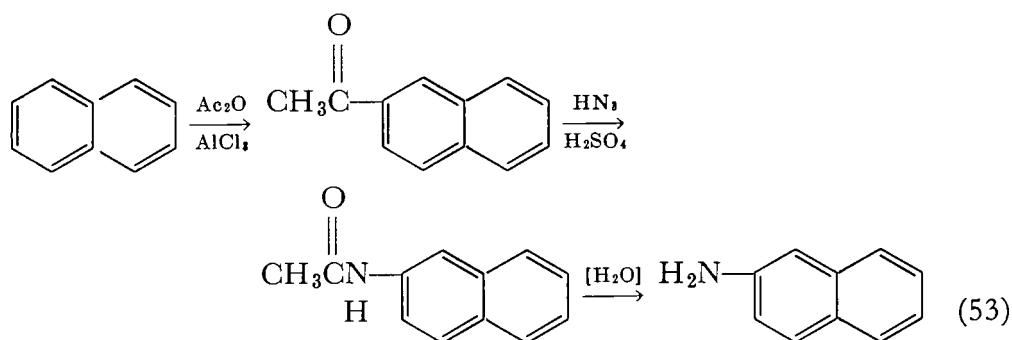


procedure applicable to nearly all types of carboxylic acids, but its usefulness is obviously limited to acids not having other functional groups that would be affected by concentrated sulfuric acid. α -Amino acids do not react, so the Schmidt reaction on malonic acids stops at the amino acid stage and is a useful preparative method.

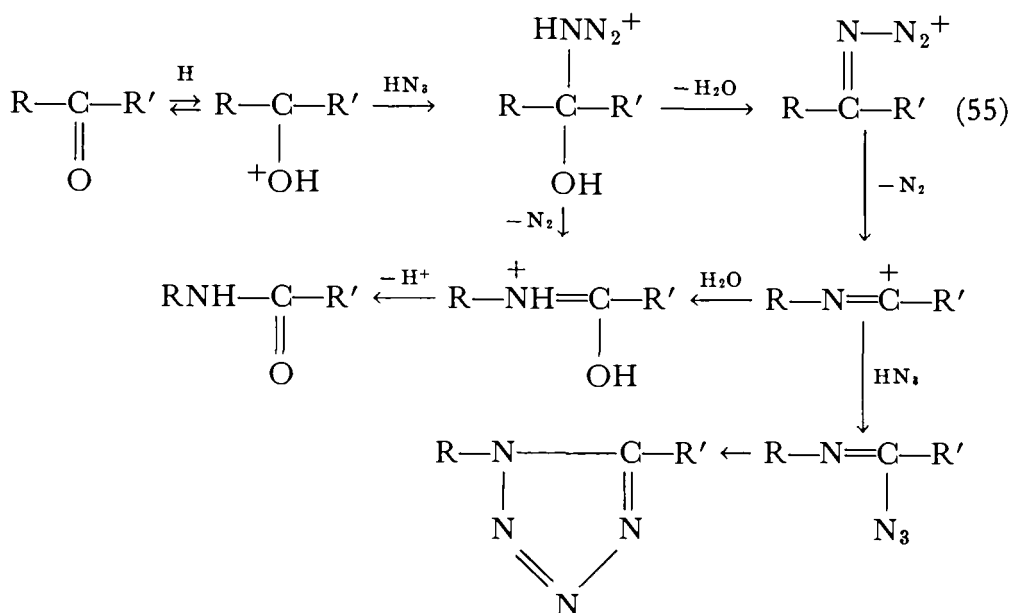
SCHMIDT REACTION WITH ALDEHYDES AND KETONES The reactions of HN_3 with aldehydes and ketones are also known as Schmidt reactions. Amides are produced from ketones (see "Preparation of primary amines," Chapter 2), and nitriles (plus usually minor amounts of formamides) from aldehydes. The reactions take place under much milder conditions than the Schmidt reactions of carboxylic acids, and often go rapidly at 0° with concentrated hydrochloric acid instead of sulfuric. With unsymmetrical ketones, mixtures may be produced. In the case of aliphatic ketones, the most highly branched group becomes attached to the nitrogen (Eqs. 51, 52). Acetophenones always give acetanilides in overwhelming



yield, which makes the combination of Friedel-Crafts acetylation and the Schmidt reaction a useful alternative to nitration and reduction for the preparation of aromatic amines (Eq. 53). Benzophenones, on the other hand, show little sensitivity to *meta* and *para* substituents and give mixtures of nearly equal amounts of both possible amides (Eq. 54). *Ortho*-substituted benzophenones give mostly the amide derived from migration of the unsubstituted phenyl group to nitrogen, but some *ortho* substituents, such as carboxyl, have the opposite effect, apparently owing to ring formation at an intermediate stage.

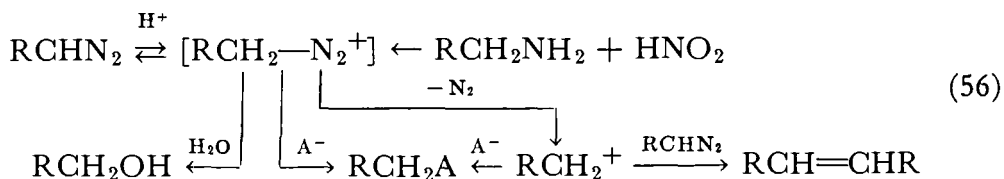


The evidence is consistent with a mechanism involving addition of hydrogen azide to the conjugate acid of the carbonyl compound; C—to—N migration with loss of nitrogen may then take place before or after dehydration,^{20, 49} according to structure and conditions (Eq. 55). Amides may thus arise directly or when the iminocarbonium ion resulting from dehydration and rearrangement subsequently combines with water. As would be expected, other nucleophiles than water can react, and if they are present during a Schmidt reaction, products other than amides may arise. Hydrogen azide is of necessity always present and can act as a nucleophile, forming imidoyl azides, which spontaneously cyclize to tetrazoles. For this reason, tetrazoles are a common side product of Schmidt reactions carried out in a medium low in water.



The products from unsymmetrical ketones may be determined by relative migration aptitudes, as appears to be the case with many aliphatic ketones, or by steric effects on the geometrical isomerism of the iminocarbonium intermediate, as appears to be the case with most diaryl ketones.^{20, 49} It is presumed that in the latter case migration of R from C to N is simultaneous with loss of nitrogen, and that the group *trans* to the departing N₂ is the one that migrates, in analogy to the Beckmann rearrangement. Migration aptitudes would be expected to operate in rearrangement of the tetrahedral intermediate, but might also do so in rearrangement of the iminocarbonium ion if the dehydration step is reversible and establishes equilibrium relatively rapidly.

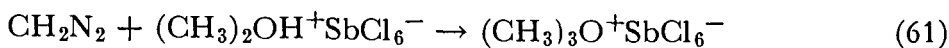
DIAZO COMPOUNDS AND ACIDS^{2b} Diazo compounds are much more sensitive to acids than are azides, and even weak acids such as acetic will react rapidly with diazomethane. If the acid is in dilute water solution, the principal product is the alcohol corresponding to the diazo compound, although anions in the solution are also taken up. Protonating the carbon of a diazo compound gives a transient diazonium ion, the same as obtained from the corresponding amine and nitrous acid, and the products are in general the same for the two reactions (Eq. 56). The diazonium



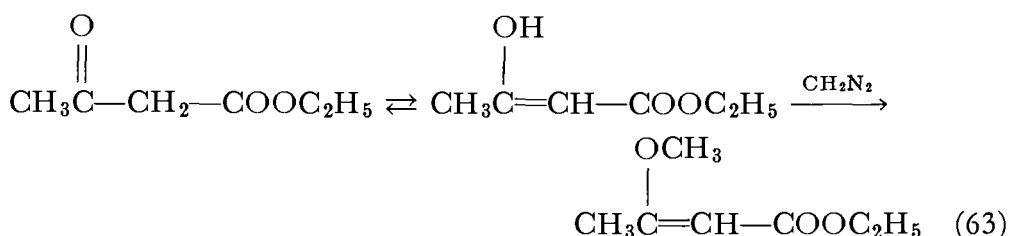
ion may first decompose to a carbonium ion before reacting with nucleophiles, or may undergo bimolecular displacement, depending on its structure and the conditions (see Chapter 2).

In dilute solutions, where the acid is not used up because most of the reaction goes to alcohol, the rate of nitrogen evolution is proportional to the pH of the solution. The reaction has actually been proposed as an accurate means of measuring acidities. With diazomethane and its close relatives, it appears that there is a rapid acid-base equilibrium, followed by a slower reaction that evolves nitrogen. The rate of the slow second step must depend on the concentration of diazonium ion, $R_2CHN_2^+$, which in turn depends on the concentration of the acid taking part in the prior equilibrium. The evidence for this is that the rate of reaction of diazoacetic ester, for example, is faster with $EtOD_2^+$ than with $EtOH_2^+$, and the product, $EtOCH_2COOEt$, contains deuterium in the α -position.⁵⁰ With some diazo compounds, such as diphenyldiazomethane,⁵¹ it has been proposed that the diazonium ion decomposes as fast as it is formed, so that the rate of reaction is then controlled by the rate of protonation of the diazo compound. The basis for this conclusion is the fact that decomposition is slower with deuterated acids ($k_H/k_D = 3.5$ for reactions in ethanol).

The ability of diazo compounds, and particularly diazomethane, to react with acidic hydrogens is of exceptional usefulness, for by such reaction compounds can be alkylated under very mild conditions. Carboxylic acids can be converted to their methyl esters in minutes at room temperature by treatment with diazomethane (Eq. 57), and purification of the product is exceptionally easy because the only other substance produced is nitrogen. Phenols react more slowly, producing aryl ethers (Eq. 58). Alcohols react too slowly for usefulness unless a catalyst is used; aluminum alkoxides,⁵² $Al(OR)_3$, or fluoboric acid⁵³ (Eq. 59), are effective, and small amounts of toluenesulfonic acid⁵⁴ can be used. Even ammonium⁵⁵ and oxonium⁵⁶ salts can be methylated with diazomethane (Eqs. 60, 61). The anion must be a poor nucleophile, such as ClO_4^- , BF_4^- , etc. to permit N-alkylation; chlorides produce principally alkyl chloride. On the other hand, *p*-toluenesulfonic acid and diazomethane give much polymethylene along with the expected ester when brought together in an inert solvent⁵⁷ (Eq. 62).

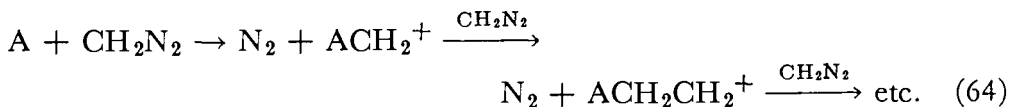


Diazo compounds may react directly with the undissociated form of weak acids, probably through initial hydrogen bonding at the diazo carbon. The anions and diazonium ions that result from the completed proton transfer are highly reactive, of course, and show a tendency to react further with each other before they can become separated by diffusion. As a result, alkylation may take place predominantly at the same site that provided the proton if conditions are favorable. Enol forms are clearly more reactive than the corresponding keto forms, and alkylation of keto-enol tautomers in equilibrium usually gives almost entirely enol ether ⁵⁷ (Eq. 63). This may be due either to the greater acidity of the enol, or to a general preference for cations to react at the oxygen atom of enolate ions. There must be some relationship between the position of

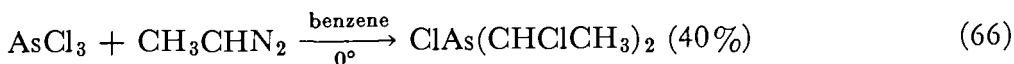
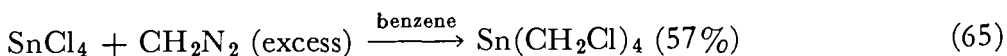


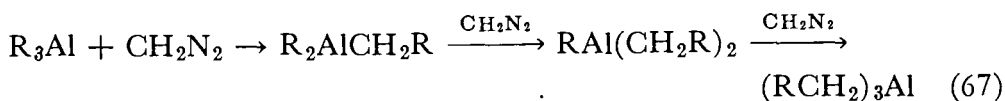
keto enol equilibrium and site of alkylation, however, for saccharin gives only N-methylsaccharin when alkylated in the solid state, where it is all in the keto form, but gives 10% O-methylation in concentrated ether solution, and 24% O-methylation in dilute ether solution with slow addition of diazomethane.^{58, 59}

LEWIS ACIDS Lewis acids in general react with diazo compounds, but the products vary considerably. Boron compounds (BX_3 , BR_3 , B(OR)_3) convert diazomethane to a high polymer,⁶⁰ $(\text{CH}_2)_x$, probably by an ionic chain reaction in which carbonium ions react with more diazoalkane (Eq. 64). Anhydrous halides of elements of the second and higher periods

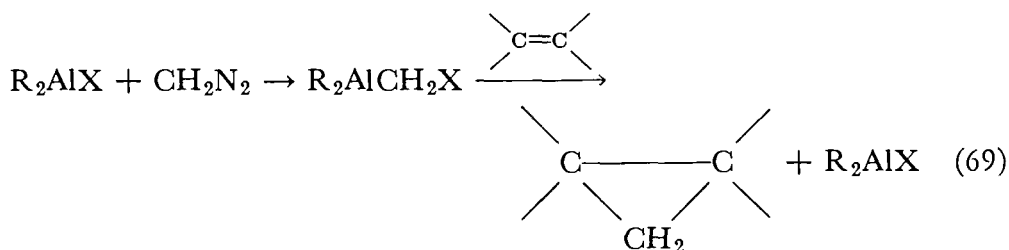


are converted in wide variety to halomethyl derivatives by diazomethane ^{61, 62} (Eqs. 65, 66). Presumably the first step is coordination of the positive atom with the diazo carbon, perhaps through *d*-orbitals, followed by loss of nitrogen and migration of halogen to carbon. Alkyl aluminums behave analogously ^{61a} (Eqs. 67, 68).

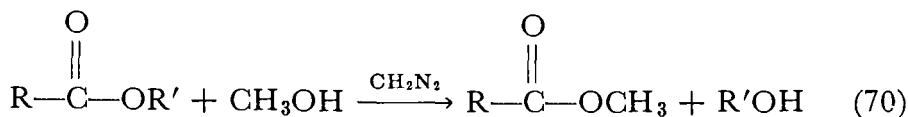




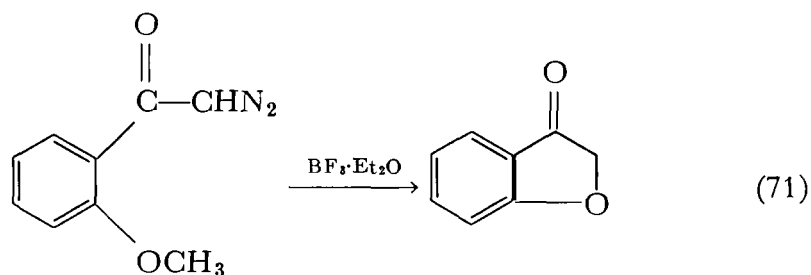
The haloalkyl organometallic compounds are highly reactive, and in particular, react readily with olefins and acetylenes to produce cyclopropanes and cyclopropenes, regenerating the metal halide. For this reason, some metal halides can be used as catalysts for the addition of the alkylidene moiety of diazoalkanes to unsaturated compounds ^{61a} (Eq. 69). Although the products are the same as those obtained from photolysis or thermolysis of the diazoalkane in the presence of the olefin, which involves carbenes, the mechanism is probably different.



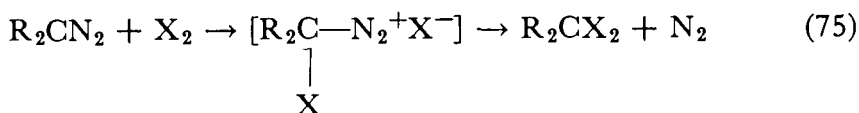
CH₂N₂ AND ESTERS It has long been known that diazomethane will cleave esters, particularly aryl esters. It was originally assumed that the reaction proceeded through hydrolysis of the aryl esters by traces of water, followed by methylation of the acid released. Subsequently, it was demonstrated that hydrolysis is quite unnecessary, and that diazomethane actually functions as a transesterification catalyst on mixtures of an ester and an alcohol ^{63a} (Eq. 70). The process is most efficient when methanol is used as the alcohol, although diazomethane will, indeed, catalyze the formation of ethyl esters when ethanol is used. It provides a gentle means of converting a wide variety of esters into their methyl counterparts. Only catalytic amounts of diazomethane (up to 25%) are required, and amides can also be cleaved if they are derived from amines that are extremely weak bases. It has been suggested that the catalysis results from the increase of the nucleophilicity of the alcohol oxygen as a result of coordination of the hydrogen with the diazomethane carbon.



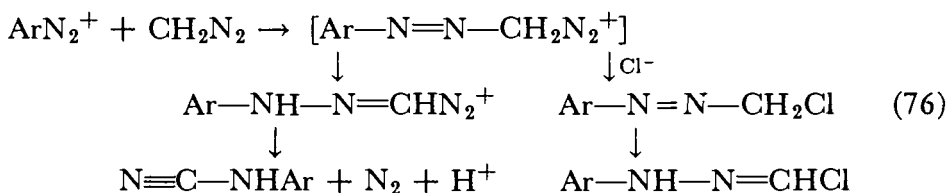
The cleavage of ethers, which has been observed as an intramolecular reaction with some alkoxy-substituted diazomethyl ketones ^{63b} (Eq. 71), is catalyzed by strong acid and is evidently unrelated to ester cleavage.



HALOGENS Halogens (Cl_2 , Br_2 , I_2) can also react as Lewis acids. Although they do not affect the azido group, they react readily with the diazo group, giving *gem*-dihalides ⁶⁶ (Eq. 75). This is one of the best methods for obtaining such compounds. It is likely that an ionic α -halo-diazonium intermediate is involved.

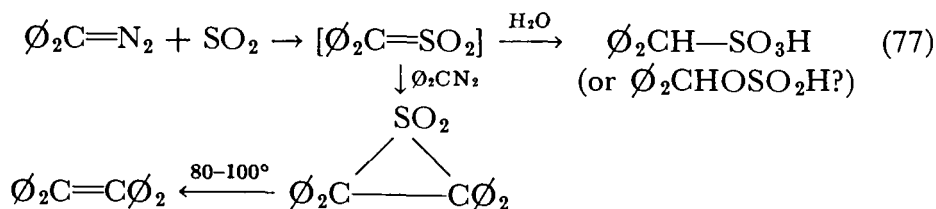


DIAZONIUM SALTS The aryl diazonium ion, ArN_2^+ , attacks diazoalkanes in the same initial manner as other electrophiles, coupling with the carbon. The presumed initial products, $\text{ArN}_2\text{CR}_2\text{N}_2^+$, have not been detected. They apparently react rapidly in two ways. By loss of nitrogen and combination with the anion that must be present, azo compounds (or the tautomeric hydrazones) are produced, which tautomerize to hydrazone derivatives if the diazo compound has an α -hydrogen ⁶⁷ (Eq. 76). When tautomerization is prevented, α -chloro azo compounds

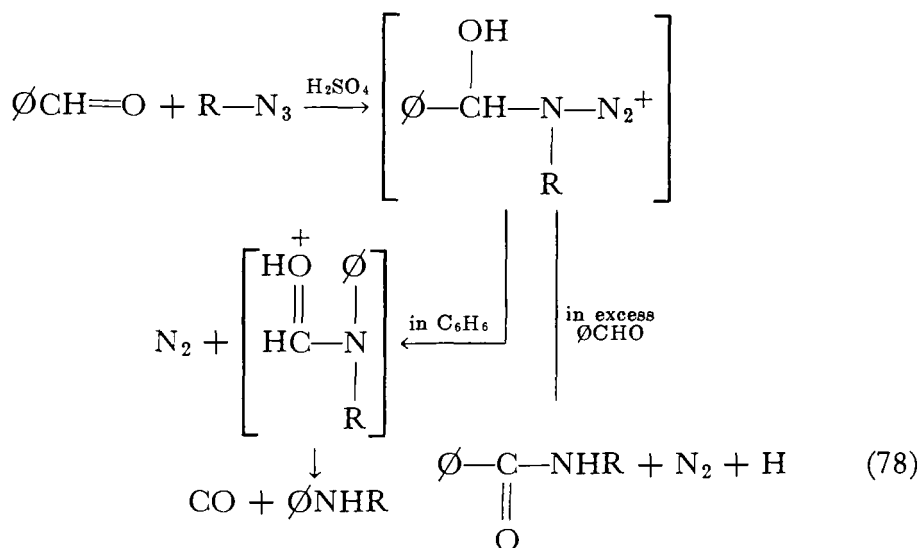


are isolated.^{2a} The reaction with the anion (e.g., Cl^-) must, of course, compete with solvolysis if a hydroxylic solvent is used.^{2a} Indeed, in dilute methanol solution, diazomethane gives rise to the methoxy analogs, methyl *N*-arylformohydrazonates, $\text{CH}_3\text{O}-\text{CH}=\text{N}-\text{NHA}r$, but if the solution is saturated with lithium chloride, the hydrazoneyl chloride again becomes the principal product.^{67b} The second type of behavior involves rearrangement with loss of nitrogen, producing a cyanamide (which may become alkylated by more diazo compound). By means of tagging experiments with ¹⁵N, it has been established that the rearrangement takes place by migration of an anilino group from N to C.^{67b}

SULFUR DIOXIDE The reaction of diazoalkanes with sulfur dioxide is of uncertain mechanistic classification, but may be related to the foregoing reactions as another case of electrophilic attack. The initial products are sulfenes,⁶⁸ which easily undergo further transformation (Eq. 77), and have not themselves been isolated.



ALDEHYDES AND KETONES Carbonyl groups in general ⁶⁹ are inert toward azides below their decomposition points and in the absence of strong acids. Even in the presence of strong acid catalysts, azides apparently react readily only with aldehydes. When equimolar quantities of reactants are used, benzaldehyde is converted to alkyl anilines by alkyl azides, but when an excess of benzaldehyde is used as a solvent, the products are benzamides ⁶⁹ (Eq. 78); yields are generally low, and replace-

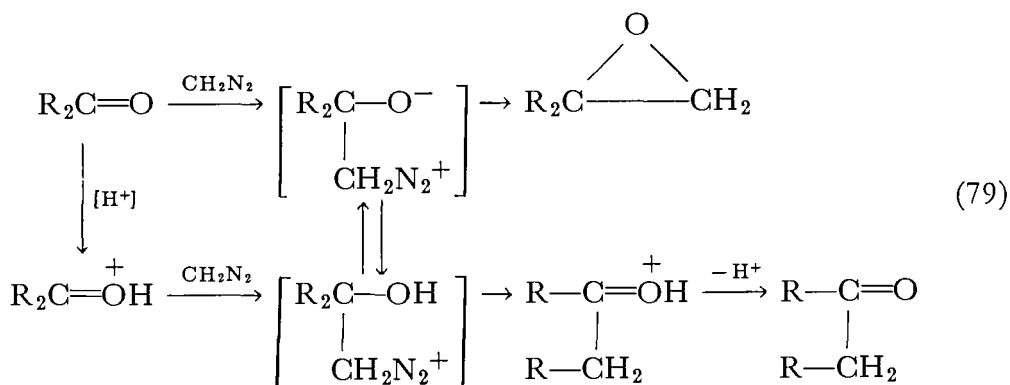


ment of the azido group by hydrogen may also occur. ^{69b} The mechanism is imperfectly understood, but presumably involves electrophilic attack by the protonated aldehyde; the divergence in reaction paths is probably related to the great difference in the proton-donating ability of the respective environments. Ketones are in part cleaved by alkyl azides and strong acid.

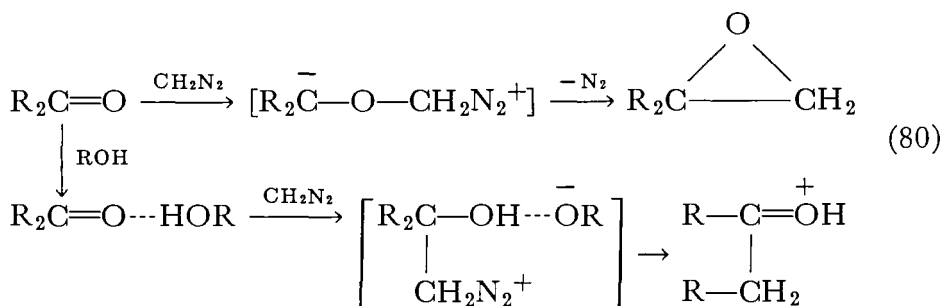
In contrast to azides, diazoalkanes react with most aldehydes and ketones (and also acid chlorides and anhydrides) even in the absence of acids, if hydroxylic substances (water, alcohols) are present. This marked difference in reactivity between azides and diazoalkanes is apparently another manifestation of the difference in susceptibility of the two functions to electrophilic attack. In general, there are three types of products—homologated ketones and aldehydes, epoxides (oxiranes), and β -diazo alcohols—but only the first two are commonly encountered. The relative proportions of the products are very sensitive to the reaction medium; alcohols moderately promote homologation over epoxide formation, ⁷⁰ and Lewis acids, such as aluminum chloride and boron fluoride, promote homologation to the virtual exclusion of epoxide formation. ⁷¹

Two explanations for these facts have been put forth. ^{2a, 70} In one view, the initial step is always electrophilic attack on the diazoalkane

carbon by the carbon of the carbonyl group or its conjugate acid (Eq. 79);

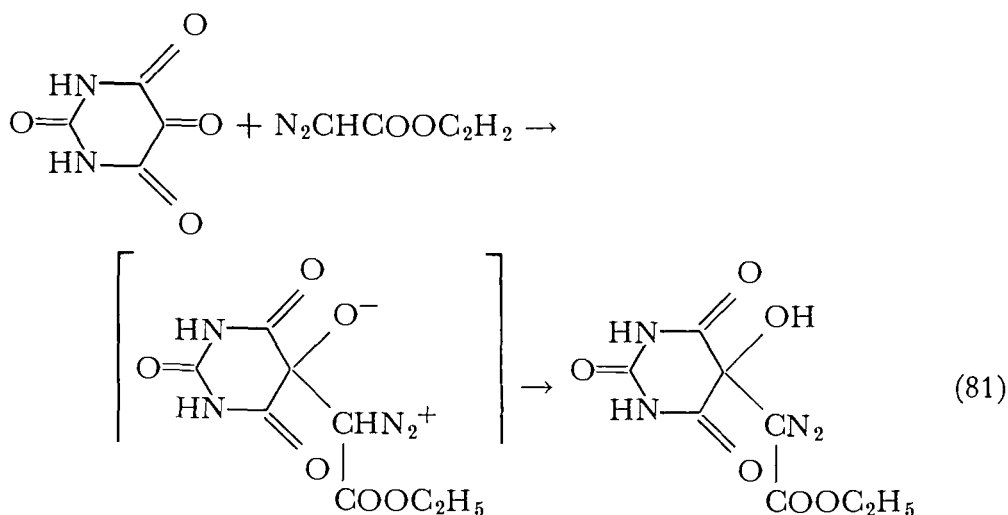


the resulting transient intermediate cyclizes to an epoxide when the oxygen is neither coordinated nor bonded to hydrogen, but otherwise undergoes rearrangement to the conjugate acid of the homologated carbonyl compound. In the other view, the oxygen of the free carbonyl compound acts as a nucleophilic site and attacks the diazoalkane carbon, producing an intermediate that can only cyclize to epoxide (Eq. 80). This reaction

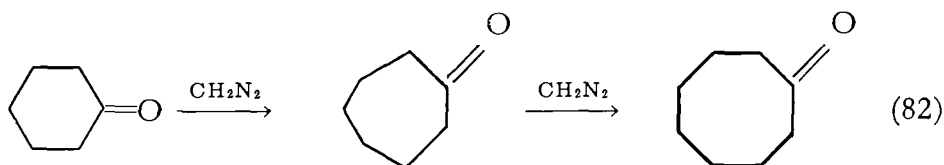


is thus uncatalyzed and presumed to be relatively slow. When the carbonyl group is converted to its conjugate acid, or even hydrogen-bonded to an alcohol, it acts as an electrophilic agent, and produces the same β -hydroxy diazonium intermediate shown in Equation 79, with the same consequences. The β -hydroxy diazonium ions are the same intermediates that are formed when β -hydroxy amines are treated with nitrous acid (see Chapter 2), a reaction that also results in rearrangement to a carbonyl compound (semipinacolic deamination).

The zwitterionic adduct of Equation 79 may also stabilize itself by internal proton transfer from the diazo carbon to the oxygen. This is only observed when a substituent is present that makes the remaining α -hydrogen more strongly acidic, as in ethyl diazoacetate ⁷² (Eq. 81).

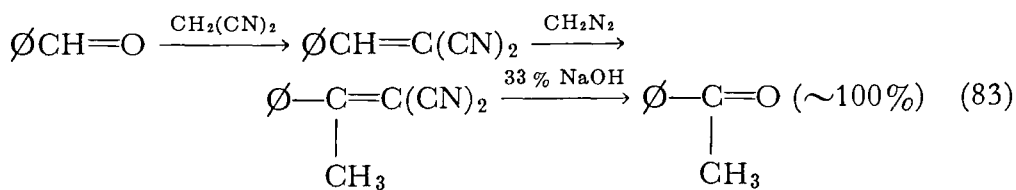


The homologation reaction is particularly useful when applied to cyclic ketones, for the ring is thereby expanded.⁷⁰ Its special value is in the synthesis of ketones with rings larger than six (Eq. 82), where direct ring closure would often be difficult. The products of diazoalkane ring expansion are, of course, themselves capable of the same reaction, since they are ketones, too, and the conditions must be chosen carefully to achieve the desired result. (An alternative that avoids multiple homologation is discussed ahead in connection with olefins.) When the diazo structure and the carbonyl group are in the same molecule, intramolecular

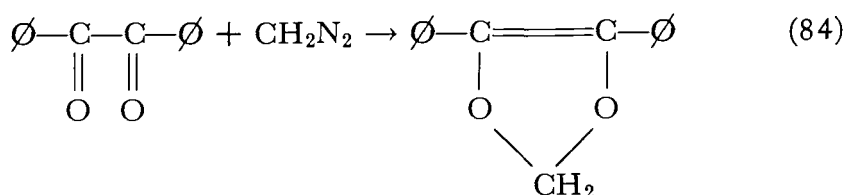


ring expansion may be possible, producing bicyclic compounds.^{73a} Optical activity resident in the migrating carbon in ring expansion is maintained,^{73b} presumably with retention of configuration.

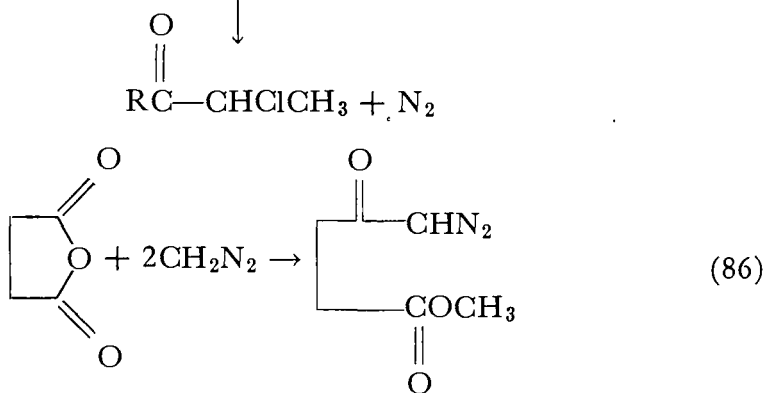
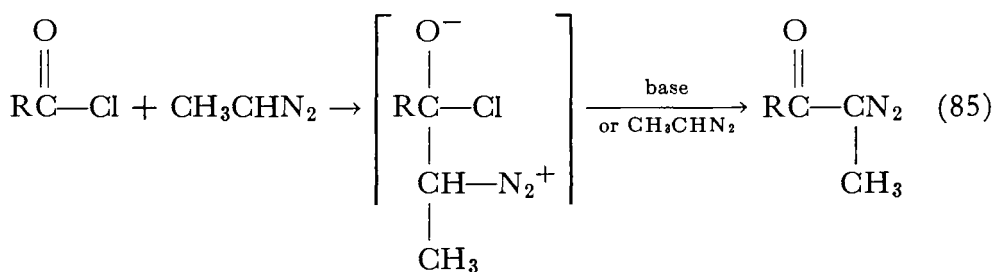
A clever way of converting aldehydes solely to methyl ketones, rather than to their mixture with epoxides and homologs, has been devised,⁷⁴ whereby the aldehyde is first condensed with malononitrile. The resulting dicyano olefins react with diazomethane to undergo methylation at the vinyl hydrogen; alkaline hydrolysis regenerates the carbonyl group (Eq. 83).



Some α -diketones, such as benzil and *o*-quinones, react at oxygen instead of carbon, producing dioxoles^{70, 75} (Eq. 84).

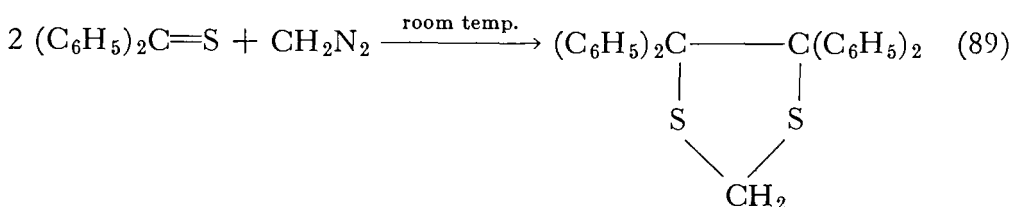
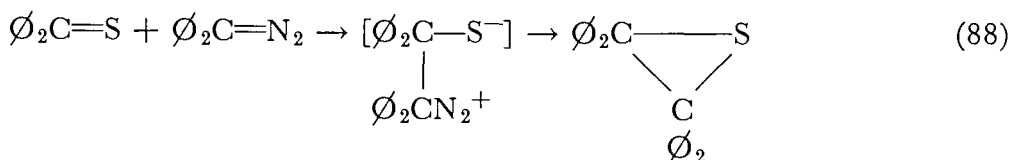
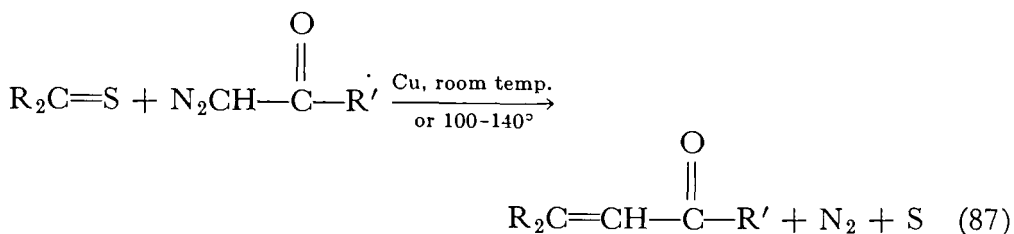


ACID CHLORIDES AND ANHYDRIDES If the carbonyl group with which a diazoalkane reacts is also attached to a potential anion, elimination may ensue, producing an α -diazo ketone.^{32, 76} This is the common reaction of acid chlorides⁷⁷ and anhydrides,⁷⁸ as long as there is a base or excess diazo alkane present to neutralize the acid produced in the elimination step (Eqs. 85, 86). If this is not the case, the acid reacts with the diazo ketone as it would with any diazoalkane, forming an ester or halide (the same product could also be formed by rearrangement of the adduct).

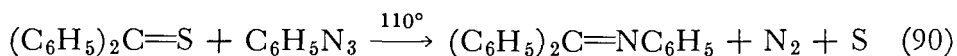


THIOCARBONYL COMPOUNDS Thiocarbonyl compounds have not been studied nearly as much as their oxygen analogs, but they show some clear differences in behavior (Eqs. 87–89). Diphenyl thiocarbonate reacts with diphenyldiazomethane to give only a thiirane, analogous to the formation of epoxides from ketones, but thiobenzophenone reacts in a 2:1 ratio with diazomethane, producing a five-membered ring, apparently through initial attack on the sulfur atom.⁷⁹ Acyl diazomethanes,

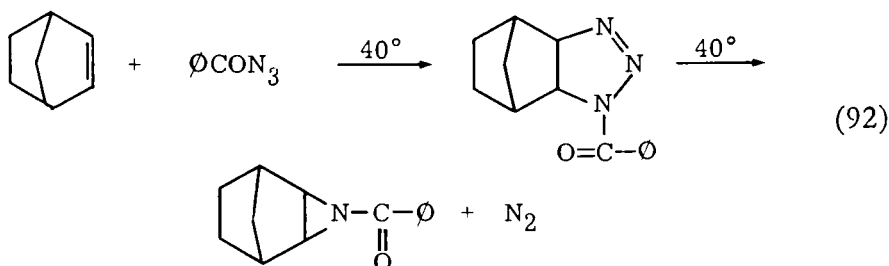
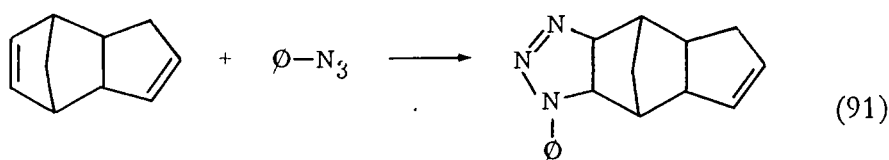
however, give α,β -unsaturated carbonyl compounds with loss of nitrogen and sulfur.^{79c} Azides characteristically react less readily, but can still



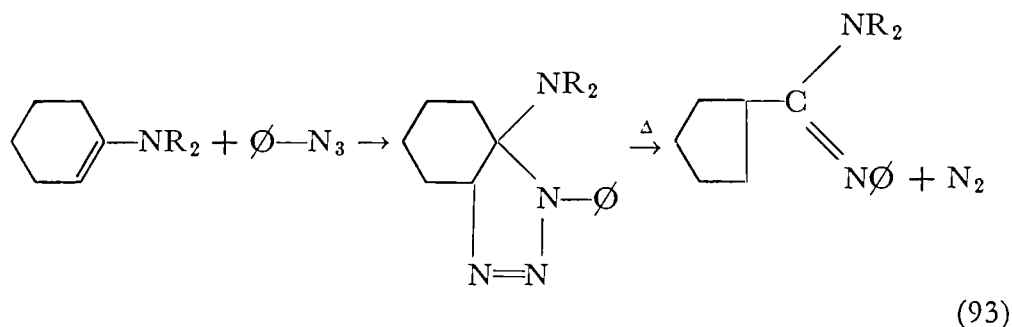
be made to react with thioketones even though they are generally inert to the oxygen analogs. Although the end products, ketimines, are different⁸⁰ (Eq. 90), the reactions may go through the same type of intermediates as the reactions of diazoalkanes, followed by loss of sulfur.



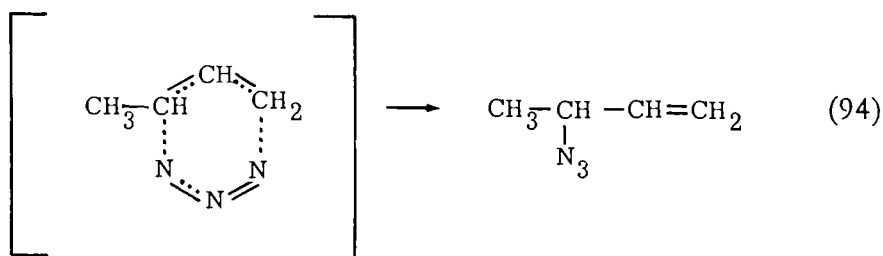
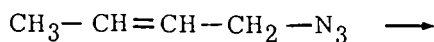
OLEFINS Carbon-carbon double bonds react with both azides and diazo compounds, principally by simple 1,3-addition to form a five-membered ring (triazoline or pyrazoline), without loss of nitrogen. The reactions are so slow with isolated double bonds, however, that such compounds can be considered sluggish toward diazoalkanes and unreactive toward azides at ordinary temperatures. Strained or conjugated double bonds are much more reactive; double bonds in bicyclic systems, such as the dimer of cyclopentadiene, add azides and diazoalkanes readily⁸¹ (Eq. 91). The difference in reactivity is so great that the occurrence of spontaneous reaction has been used as a test for strained double bonds, and phenyl azide has often been used as a reagent to convert terpenes to crystalline derivatives. With toluenesulfonyl azide, the initial adducts lose nitrogen to form aziridines almost as fast as they are formed, and the appearance of effervescence when an olefin is treated with this reagent is diagnostic of a bicyclic double bond.⁸² With benzoyl azide,^{82c} the labile pyrazoline adducts can be detected, but they decompose to aziridines even at 40° (Eq. 92) (see also p. 242).



1-Amino olefins (enamines) are also very reactive toward azides. The 5-amino triazolines that are formed are stable only when the azide is not held by a source of electron withdrawal; they lose nitrogen and undergo rearrangement to amidines on heating or spontaneously⁸³ (Eq. 93).

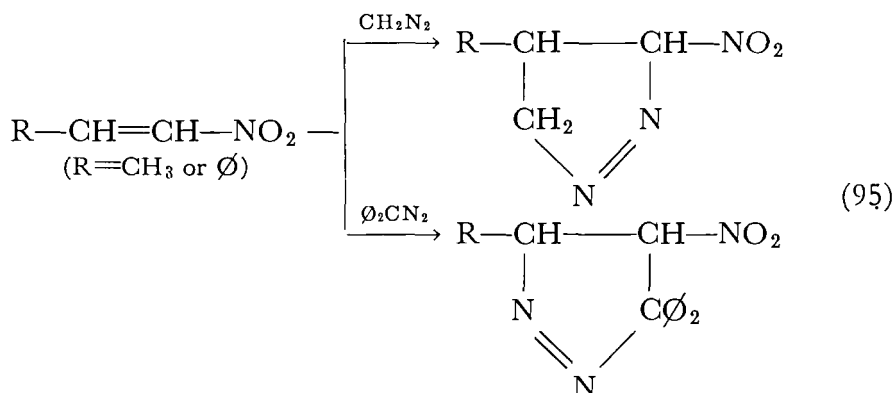


In the special case of allylic azides, intramolecular reaction of the azido group with a double bond occurs without ultimate cyclization.⁸⁴ The result is allylic isomerization, in which the original outer azide nitrogen becomes attached to carbon in the isomerized product (Eq. 94), as shown by isotopic labeling.



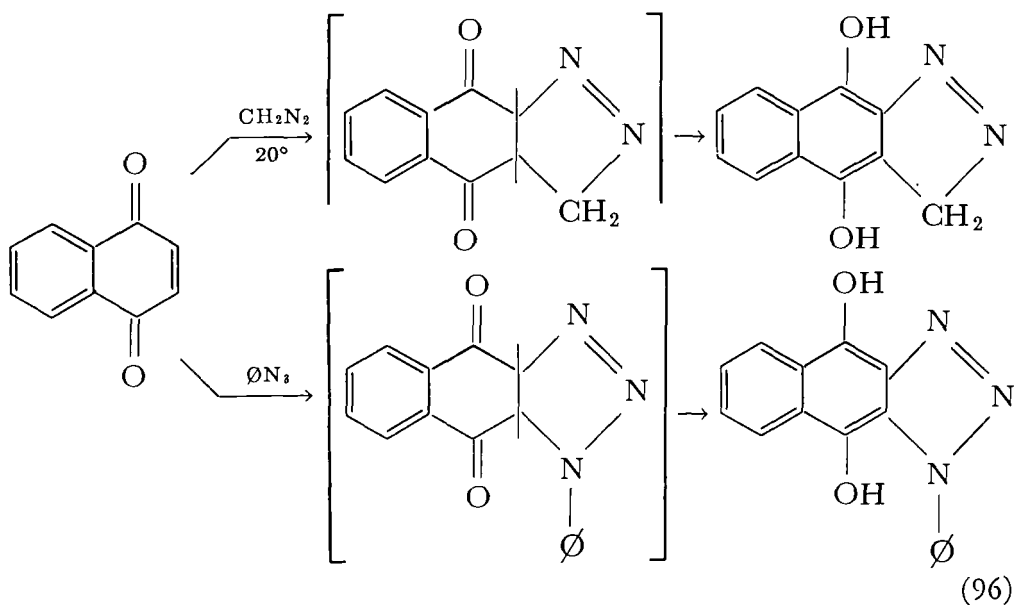
With unsymmetrically unsubstituted double bonds,⁸⁵ the direction of addition of diazoalkanes can be accounted for in most cases by the assump-

tion that the carbon of the diazoalkane is nucleophilic and attacks the double bond to give the most stable intermediate carbanion. The explanation of orientation is not quite so simple, however, for diphenyldiazomethane sometimes adds in the opposite direction from other diazoalkanes⁸⁶ (Eq. 95). A difference in mechanism from one olefin to another is suggested by the fact that addition to maleic and fumaric esters

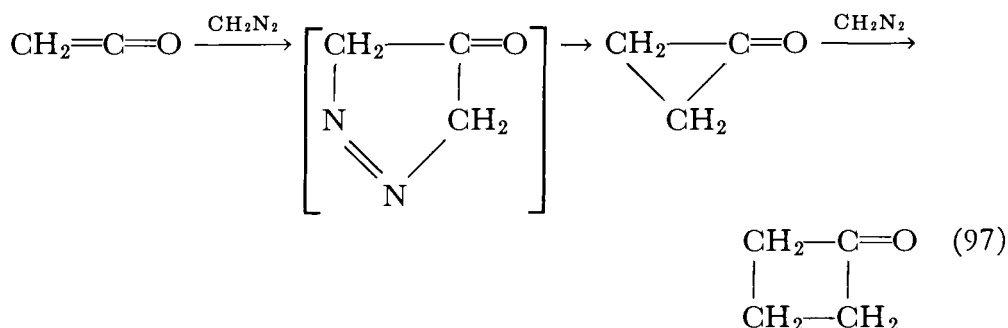


is not stereospecific, the same pyrazoline (*trans* substituted) being obtained from each,⁸⁷ whereas addition of diazomethane to ethyl α -methylcrotonate (*cis* and *trans*) is stereospecifically *cis*.⁸⁸

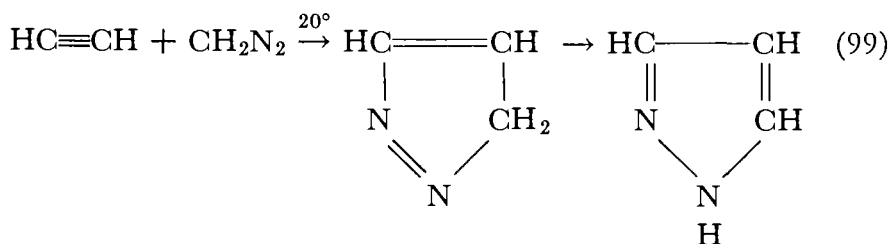
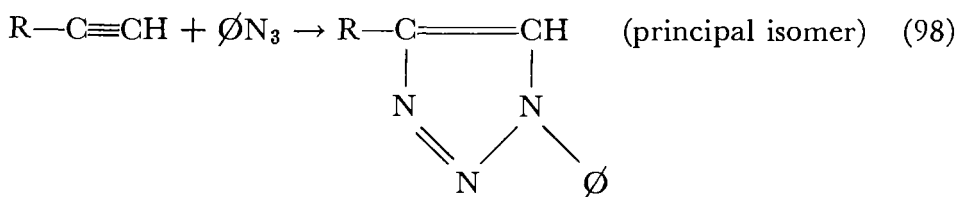
Conjugated double bonds, and especially those polarized by electron-withdrawing substituents, react fairly readily with both azides and diazoalkanes. Quinones, for example, form benzotriazoles⁸⁹ or benzopyrazoles⁹⁰ (a tautomerism follows the addition, converting the quinone system to a benzenoid system) (Eq. 96).



The adducts with olefins—triazolines and pyrazolines—generally lose nitrogen easily when warmed, in the absence of tautomerization; mercury compounds catalyze the reaction.^{87a} The products are either three-membered rings (aziridines or cyclopropanes), or the isomeric unsaturated compounds (ketimines or olefins).^{82, 83, 88, 89, 91} In many cases the triazolines and pyrazolines cannot be isolated from the reactions of azides or diazoalkanes with olefins, because they are unstable under the conditions required for the addition. A synthetically useful example of this is the reaction of diazomethane with ketene, which can be conducted so as to produce either cyclopropanone or cyclobutanone⁹² (Eq. 97).

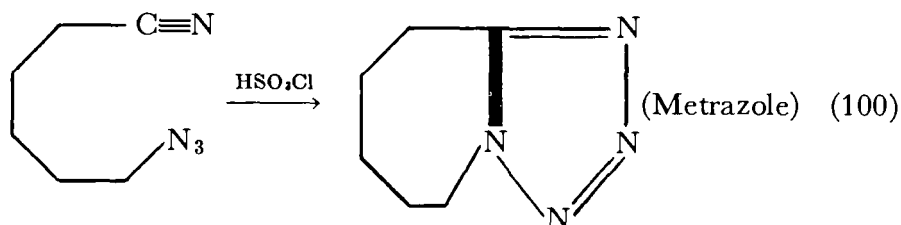


ACETYLENES Acetylenes react with azides⁹³ and diazoalkanes⁹⁴ in a manner similar to olefins. Although the reactions are often slow, they are often more successful than the corresponding additions to olefins, for the products, triazoles and pyrazoles (Eqs. 98, 99), are much more stable, which allows higher temperatures and longer reaction times to be used.

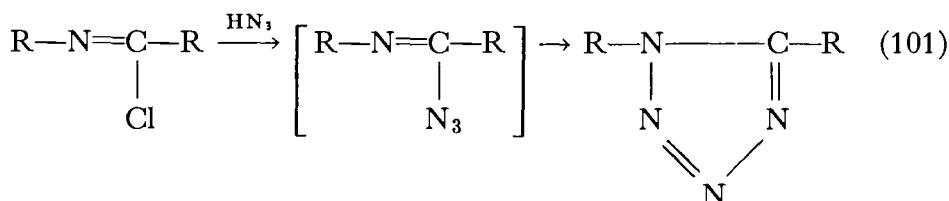


Other unsaturated systems, such as imines, nitroso compounds, azo compounds, and nitriles, also react with azides and diazoalkanes under some circumstances, but the reactions are not of as great importance. Azides (except hydrogen azide) are inert toward most such groups under

mild conditions, and reaction is usually observed only when the two groups, such as cyano and azido, are favorably situated in the same molecule⁹⁵ (Eq. 100), or when the cyano group is polarized by strongly electron-withdrawing substituents, such as perfluoroalkyl.⁹⁵

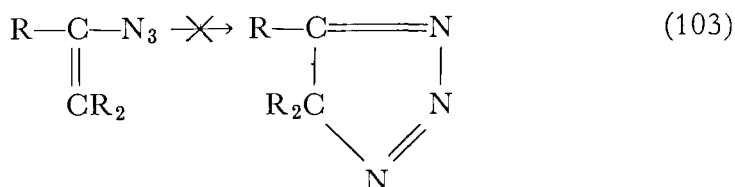
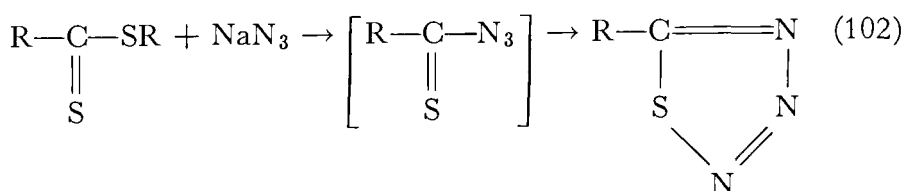


Although azides do not react with simple C—N double bonds in another molecule, imidoyl azides react intramolecularly to give tetrazoles so readily that the open structure can be isolated only in exceptional instances.^{2d} The reaction of imidoyl chlorides with hydrogen azide, which might be expected to give imidoyl azides, is in fact, the most general route to 1,5-disubstituted tetrazoles (Eq. 101) and is known as the von Braun-Rudolph synthesis.⁹⁶



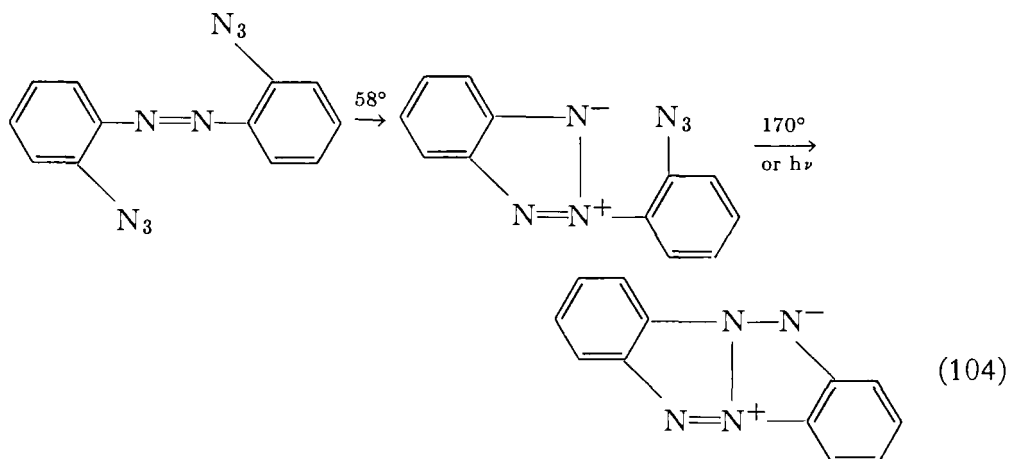
The cyclization of imidoyl azides is reversible, although the equilibrium ordinarily lies far on the tetrazole side. Electron-withdrawing substituents increase the relative stability of the imidoyl azide form, as does protonation by strong acids; steric strain arising when a tetrazole ring is fused to a previously existing five-membered ring also shifts the equilibrium toward the imidoyl azide.^{2d} The position of the equilibrium is sensitive to the polarity of the solvent, and in very polar solvents, such as dimethyl sulfoxide, the tetrazole structure (which has a relatively high dipole moment) is markedly favored.^{97a} A similar azide-tetrazole equilibrium is observed with hydroximoyl and hydrazonoyl azides.^{97b-d}

It is interesting to compare the stability toward cyclization of other functions having an azido group joined to an unsaturated carbon. Acyl azides, on the one hand, show no tendency whatsoever to cyclize to oxatriazoles, but thioacyl azides are apparently completely unstable toward the thiatetrazole structure^{97e} (Eq. 102). The few vinyl azides that have been reported apparently show no tendency to cyclize to triazolenines (Eq. 103). These observations can be correlated in terms of what is



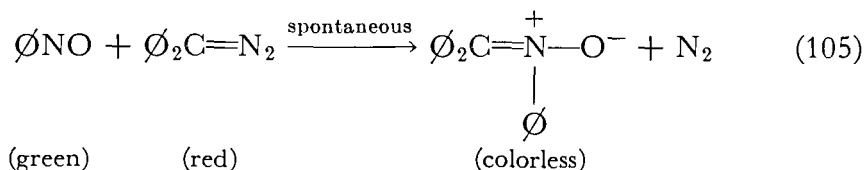
known of the relative stabilities of the double-bond systems in the open structures ($\text{C}=\text{O} > \text{C}=\text{N} > \text{C}=\text{S}$) together with the fact that the triazolenines, alone of the group of ring systems concerned, do not have the capability for a quasi-aromatic electronic structure (there being no unshared electron pair on the β -atom, a carbon).

AZIDES AND AZO COMPOUNDS The reaction of an azido group with an azo structure has been encountered only in intramolecular examples, and even then, adducts of a pentazole structure have not been detected, and, indeed, may not be formed at all. *o*-Azido azobenzenes lose nitrogen on heating and are converted to benzotriazoles. A particularly interesting example is that of *o,o'*-diazidoazobenzene, which goes to a surprisingly stable mesoionic triazolotriazole structure ^{23c} (Eq. 104).

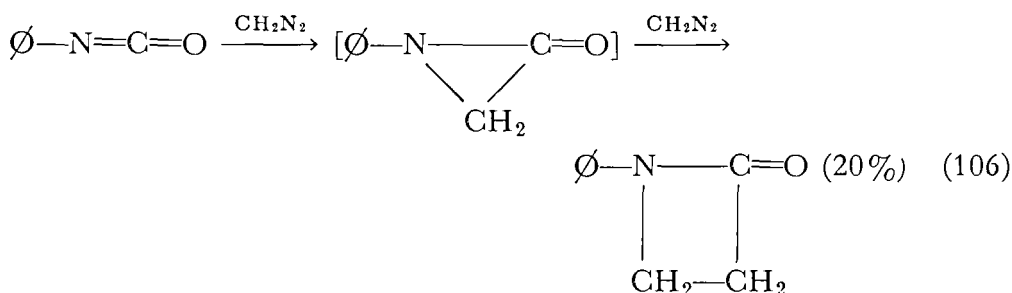


DIAZOALKANES AND NITROSO COMPOUNDS Diazoalkanes are more reactive, of course; they react most readily with nitroso compounds; the products are nitrones.⁹⁸ Nitrogen is evolved with effervescence, and owing to the intense colors of the reactants, the process can be carried out quite nicely as a titration (Eq. 105). The reaction probably begins in the same way as with carbonyl groups, but nitrogen is lost without

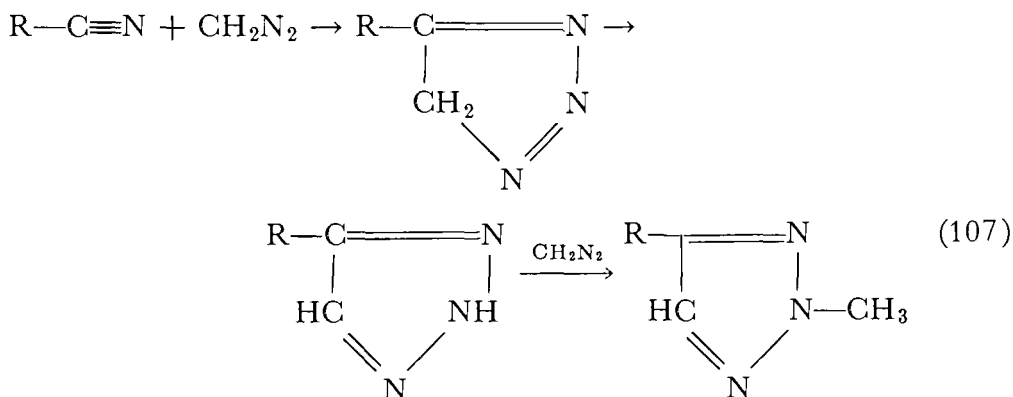
cyclization or rearrangement, owing to the availability of the unshared electron pair on the nitroso nitrogen. It is a useful preparative method (see Chapter 8). The somewhat analogous reaction of diazoalkanes with nitrosyl chloride leads to hydroximoyl chlorides.⁹⁹ The most interesting



example of reaction with a C—N double bond is that with phenyl isocyanate, which gives a β -lactam (Eq. 106), presumably in an analogous manner to the reaction with ketene.^{100a} With carbodiimides, however, nitrogen is not lost, and amino triazoles are obtained.^{100b} As with azides,

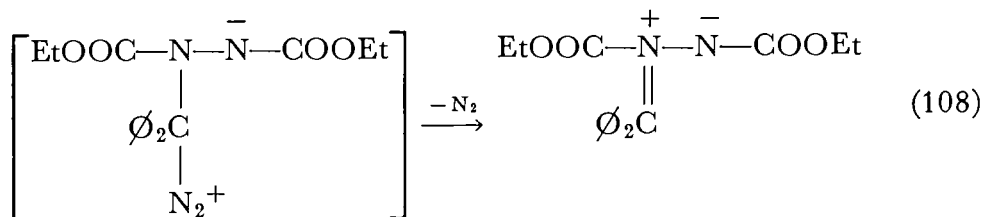
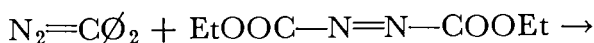


nitriles react with diazoalkanes intermolecularly only when the cyano group is activated by the presence of strong electron-withdrawing groups; triazoles are then produced¹⁰¹ (Eq. 107). Isothiocyanates simply add to form thiadiazolines.



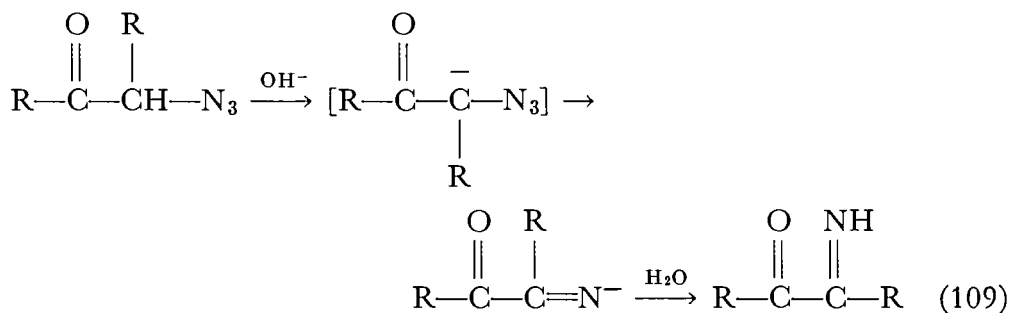
The only reported cases of the reaction of diazoalkanes with N=N double bonds involve the unusually reactive azodicarboxylic esters, whose behavior is usually that of an electrophile. The primary adducts, which

may be tetrazolines or open-chain zwitterions, have not been observed; nitrogen is lost, and diaziridines, azomethine imides, or oxadiazolines are formed ¹⁰² (Eq. 108).

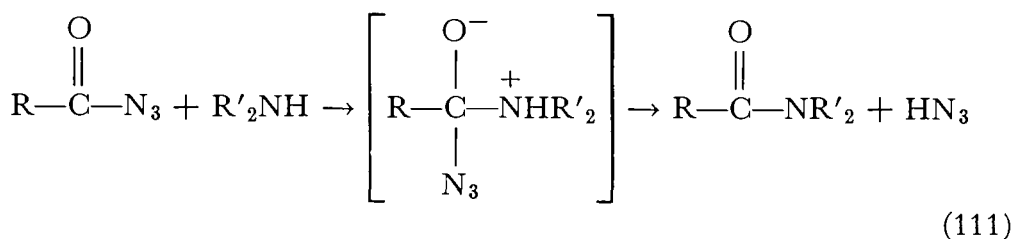
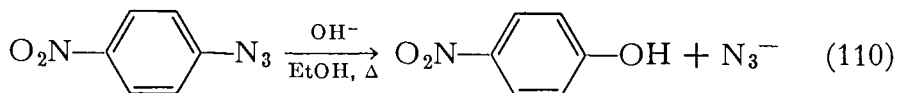


AZIDES WITH BASES Oxy-anion nucleophiles are without effect on azides, and only when the structure holding the azido group is itself susceptible to attack by bases does reaction occur with most of them. Alkyl azides are thus inert to hydrolysis, so much so that β -haloethyl azides are converted by base into vinyl azide by alcoholic alkali.¹⁰³

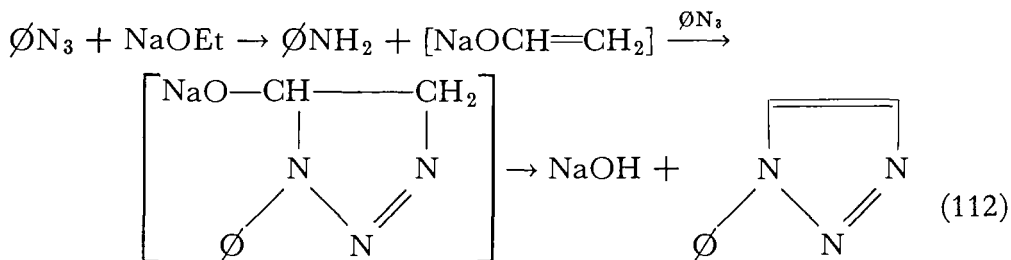
α -Azido carbonyl compounds lose nitrogen when treated with strong bases (Eq. 109), presumably because the base can remove an α -hydrogen; α -imino compounds or their transformation products are produced.^{104, 105} β -Azido ketones undergo elimination with strong bases, producing azide



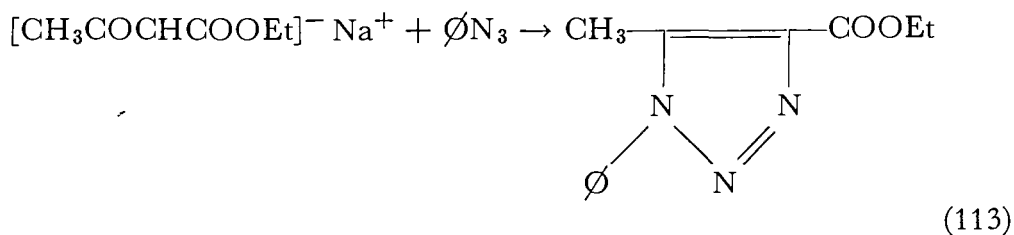
ion and an α,β -unsaturated ketone, undoubtedly through initial removal of a proton from the position α to the carbonyl.¹⁰⁶ Acyl azides, and some aryl azides ¹⁰⁷ with electron-withdrawing substituents in the *ortho* and *para* positions, undergo displacement of azide ion by most bases (Eqs. 110, 111), even moderately weak ones, in favorable cases. Such reactions are almost certainly two-step processes of addition of the nucleophile, followed by expulsion of the azide ion, analogous to the saponification of esters and amides. Acyl azides can thus function as acylating agents, not quite as reactive as anhydrides.³¹ Since they can be made under mild conditions from esters through the hydrazides, they have value as acylating agents in synthesis, such as in the preparation of peptides.



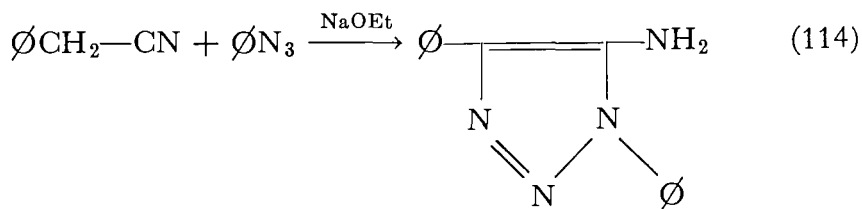
Sodium ethoxide reacts with phenyl azide,¹⁰⁸ but not as a base. The products are phenyltriazole and aniline, whose formation can be rationalized by assuming that some azide is first reduced, thereby converting ethoxide to the enolate anion of acetaldehyde; the latter can then add to more azide in the manner of other olefins (Eq. 112). Indeed, enolate salts in general react with azides to produce triazoles^{2d, 109} (Eq. 113).



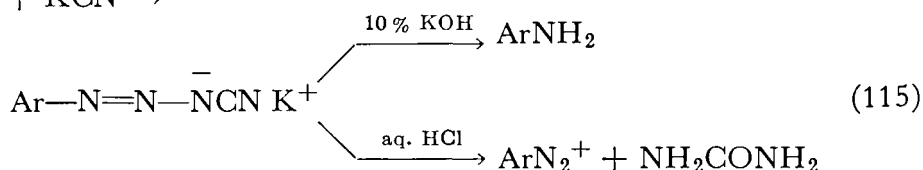
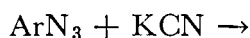
Since these reactions take place much more readily than the reaction of simple olefins with azides, it seems likely that the initial step is nucleophilic attack by a carbanion on the terminal azide nitrogen. The observed orientation is consistent with this interpretation. Even the α -anions of



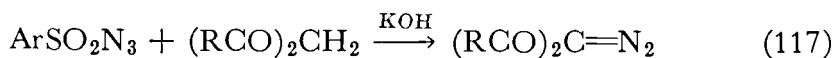
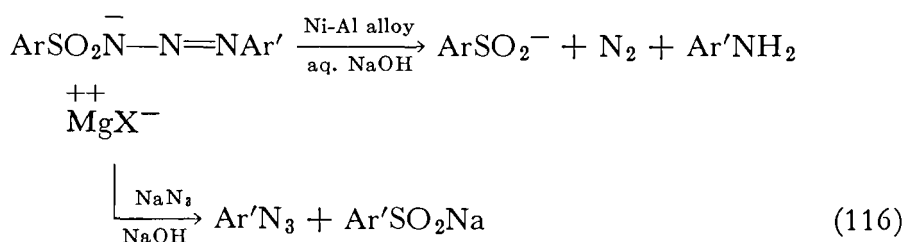
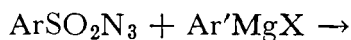
nitriles add similarly; in such cases, the stable pseudoaromatic triazole structure is attained by protopic shift rather than elimination¹¹⁰ (Eq. 114).



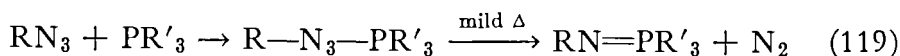
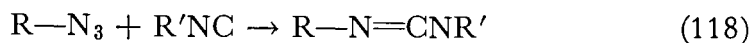
AZIDES WITH OTHER NUCLEOPHILES Nucleophilic carbon and phosphorus constitute an exception among nucleophiles in that they will react with all types of azides. Cyanide is the simplest example; reaction occurs at the unsubstituted nitrogen, producing a triazene,¹¹¹ whose hydrogen is acidic owing to the cyano group (Eq. 115). These compounds are quite reactive and are decomposed to amines by alkali and to diazonium salts and urea by acids. Grignard reagents generally react analogously,^{2d, 112} forming disubstituted triazenes (although α -azidosuccina-



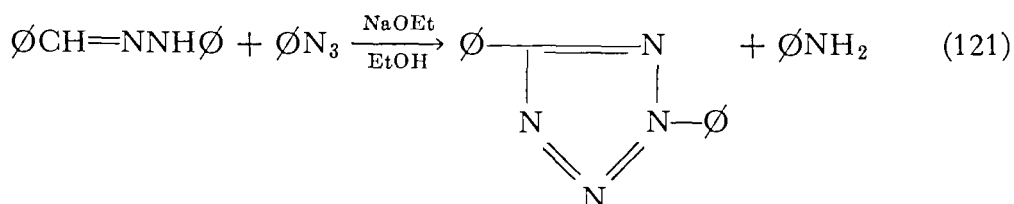
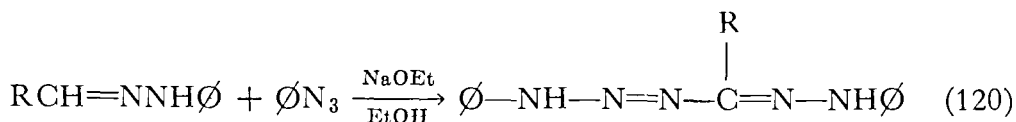
mides are claimed to give secondary amines instead¹¹³). The dialkyl (or aryl) triazenes are of low stability, and often only their decomposition products can be isolated. Sulfonyl azides, however, give rise to more stable triazenes, especially with aryl Grignard reagents, in which case they can then be reduced to amines or cleaved to aryl azides¹¹⁴ (Eq. 116). This is one of the few preparatively useful methods for converting a Grignard reagent to an amine. Similarly, carbanions of active methylene compounds can be converted to diazo compounds (Eq. 117).¹¹⁵ Iso-cyanides react with azides to form carbodiimides¹¹⁵ (Eq. 118). Phosphines^{114, 116, 117} attack azides to give analogous end products; the phos-



phazines, which are produced first, can sometimes be isolated, but they lose nitrogen spontaneously to form phosphine imines (Eq. 119). Hydrazones of aldehydes in the presence of sodium ethoxide give analogous



products if it is considered that attack is by the carbanion derived from the aldehyde carbon ¹¹⁸ (Eq. 120). In the case of benzaldehyde phenylhydrazone, the initial adduct apparently undergoes cyclization accompanied by N—N bond cleavage ¹¹⁹ (Eq. 121).

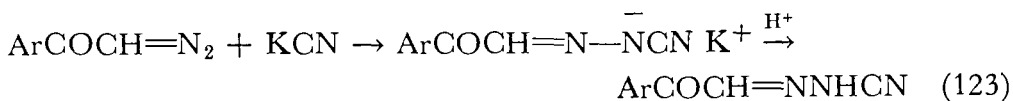


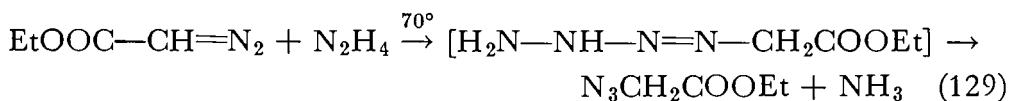
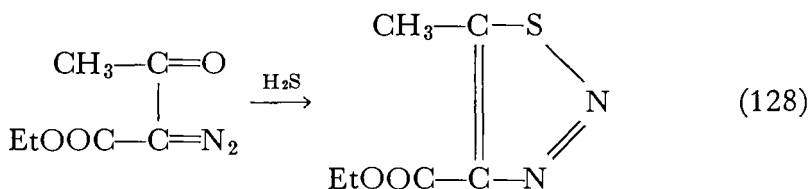
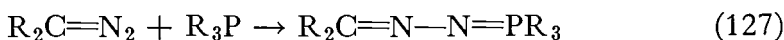
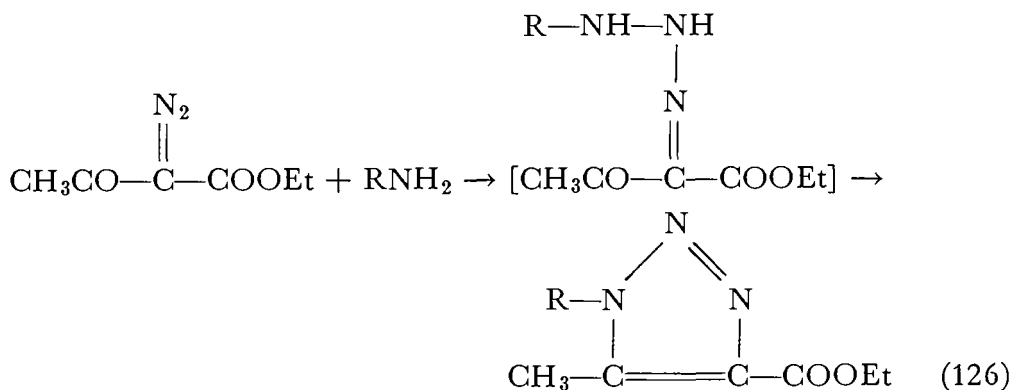
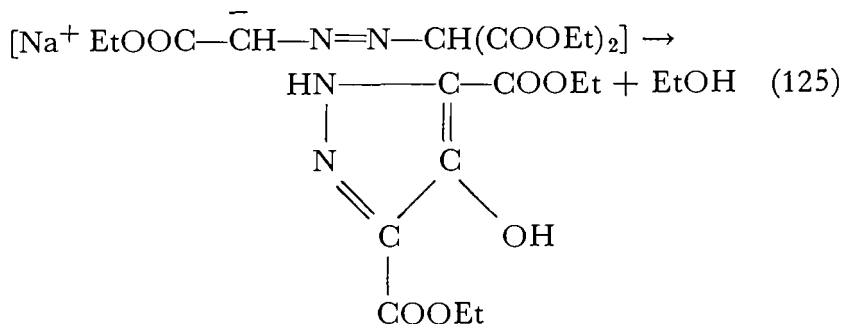
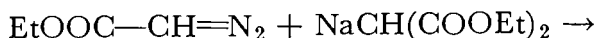
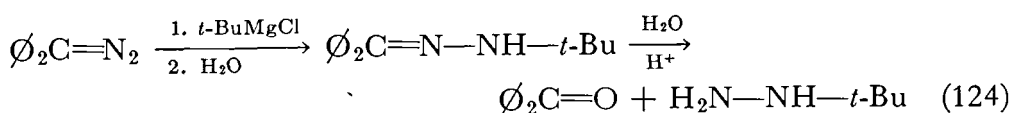
DIAZO ALKANES AND BASES Diazoalkanes are largely inert to strong base, just as are azides, and are in fact often prepared by reactions that require the presence of alcoholic alkali. A hydrogen on a diazomethane carbon has a latent acidity, however, and in one case, diazomethane reacting with methyllithium ¹²⁰; this has resulted in salt formation (Eq. 122) (the reaction of this salt to produce isodiazomethane was men-



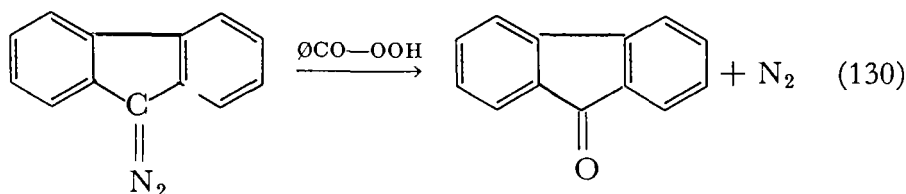
tioned earlier in this chapter). The presence of an acyl group would be expected to increase the acidity of a diazomethane hydrogen, so it is not surprising to learn that α -diazoketones react vigorously with sodium methoxide. Diazoacetophenone thus gives rise to a complex mixture of pyrazoles, triazoles and tetrazoles, of which 5-benzoyltetrazole (yield 10%) is the largest single component.¹²¹

STRONG NUCLEOPHILES Diazoalkanes are in general more reactive toward nucleophilic attack at the terminal nitrogen than are azides, however, and in addition to cyanide ¹²² and other carbanions,¹²³ Grignard reagents,¹²⁴ phosphines,¹²⁵ amines,¹²⁶ hydrazines,^{126, 127} sulfites,¹²⁸ and sulfide ¹²⁹ may react with diazoalkanes in this way (Eqs. 123–129). Potassium cyanide produces cyanohydrazone salts (Eq. 123), analogous to the reaction with azides. Similarly, Grignard reagents produce alkylhydrazones (Eq. 124) (which may react further). Hydrolysis of the products so obtained constitutes a useful hydrazine synthesis. The reaction with sulfide more often leads to alkylation or reduction.¹³⁰

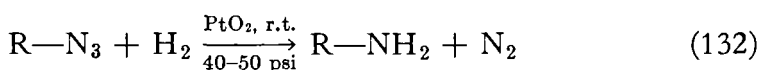
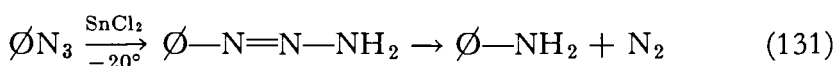




OXIDATION; REDUCTION Oxidizing agents do not affect the azido group,¹³¹ but diazoalkanes are attacked by lead tetraacetate^{132a} and by peroxybenzoic acid^{132b}; nitrogen is eliminated and the carbon becomes a carbonyl group (Eq. 130) (or the corresponding *gem*-diacetate). *tert*-Butyl hypochlorite has been reported to convert diazomethane to a chloro derivative, which was obtained in solution only.¹³³ Reduction, on the

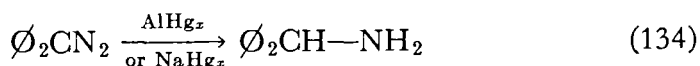
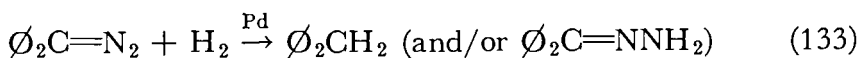


other hand, can be brought about on both azides and diazoalkanes by a variety of reagents ² (Eqs. 131, 132). The usual product with azides is the corresponding amine, nitrogen being evolved. This type of reduction has been brought about by catalytic hydrogenation,¹³⁴ tin or zinc and acid, sodium and alcohol, hydrogen bromide or iodide,^{44, 135} lithium aluminum hydride,¹³⁶ sodium borohydride¹⁵ in hot isopropanol, and sodium dithionite,¹³⁷ among others. With delicate handling, triazenes, $\text{R}-\text{N}=\text{N}-\text{NH}_2$, can sometimes be isolated.^{138, 139} As they decompose spontaneously into amine and nitrogen, they may be general intermediates for most azide reductions. In only one case, α -naphthyl azide, has

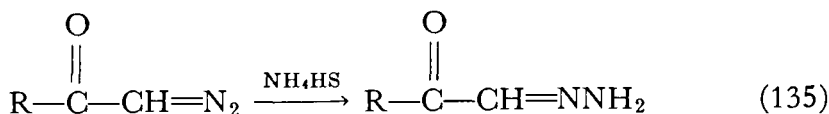


reduction to a hydrazine been reported.¹³⁸ The general ease of the reduction has led to increasing use of it in the preparation of primary amines.

Complete reduction of diazoalkanes gives a hydrocarbon (Eq. 133), in analogy to the reduction of azides. Catalytic hydrogenation is the most successful method,¹⁴⁰ but reduction of diazoalkanes has not been as widely studied as that of azides, probably because the conversion of diazoalkane to hydrocarbon is not a profitable reaction from a preparative standpoint. Hydrazones, hydrazines and amines (Eq. 134) have also been obtained with other reducing agents, such as the amalgams of

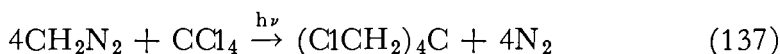
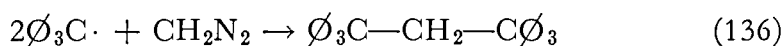


sodium or aluminum ¹⁴⁰⁻¹⁴²; hydrazones are formed in good yield when ammonium sulfide ¹⁴¹ (Eq. 135) or lithium aluminum hydride ^{2a} is the reducing agent. Even hydrogen sulfide may reduce diazo compounds

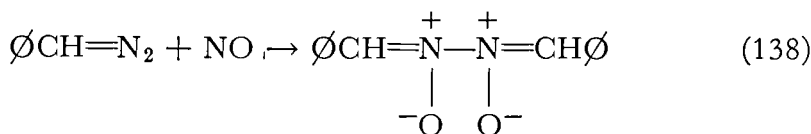


in preference to becoming alkylated¹³⁰; this behavior appears to be favored by the presence of electron-withdrawing groups, which repress the protonation that is presumably required in the first step of alkylation. Accordingly, diazoacetophenone and diazoacetic ester undergo reduction by hydrogen sulfide almost exclusively. The reduction of *ortho*-diazooxides to phenols by heating in the presence of benzylamine or benzyl alcohol is probably a special case, involving preliminary carbene formation.²⁷

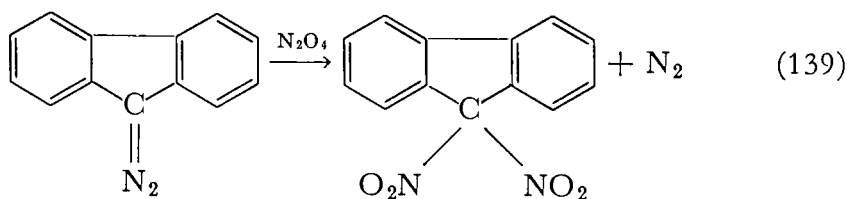
FREE RADICALS Azides appear to be inert toward free radicals, judging from the failure of triphenylmethyl radicals to interfere with the rearrangement of acyl azides. On the other hand, *tert*-butyl hydroperoxide induces decomposition of benzenesulfonyl azide and its attack on xylene to give a sulfonamide.^{117b} Diazomethane, however, does react with triphenylmethyl radicals, losing nitrogen and forming 1,1,1,3,3,3-hexaphenylpropane¹⁴³ (Eq. 136). The photochemical reaction of diazomethane with carbon tetrachloride, which gives tetrachloroneopentane (Eq. 137), has been reported to be a free-radical chain reaction.¹⁴⁴



The reactions of diazoalkanes with nitric oxide and nitrogen dioxide come in the category of radical reactions, although there is justification for interpreting the reaction of the latter reagent as electrophilic attack (by NO_2^+ , actual or potential). Phenyldiazomethane reacts with nitric oxide to form an azine N,N' -dioxide¹⁴⁵ (Eq. 138), a structure of unusual interest because of the apparent presence of positive charges on adjacent atoms (but compare the discussions of structure in Chapters 11 and 13). The azine dioxides react readily with excess nitric oxide to form an



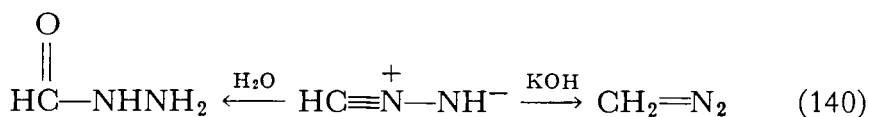
aldehyde (or ketone) accompanied by the corresponding nitrimine, $\text{R}_2\text{C}=\text{N}-\text{NO}_2$. Nitrogen dioxide converts diazo compounds to *gem*-dinitro compounds, as shown by the example of 9-diazo fluorene¹⁴⁶ (Eq. 139). The photolytic reaction of diphenyldiazomethane with oxygen,



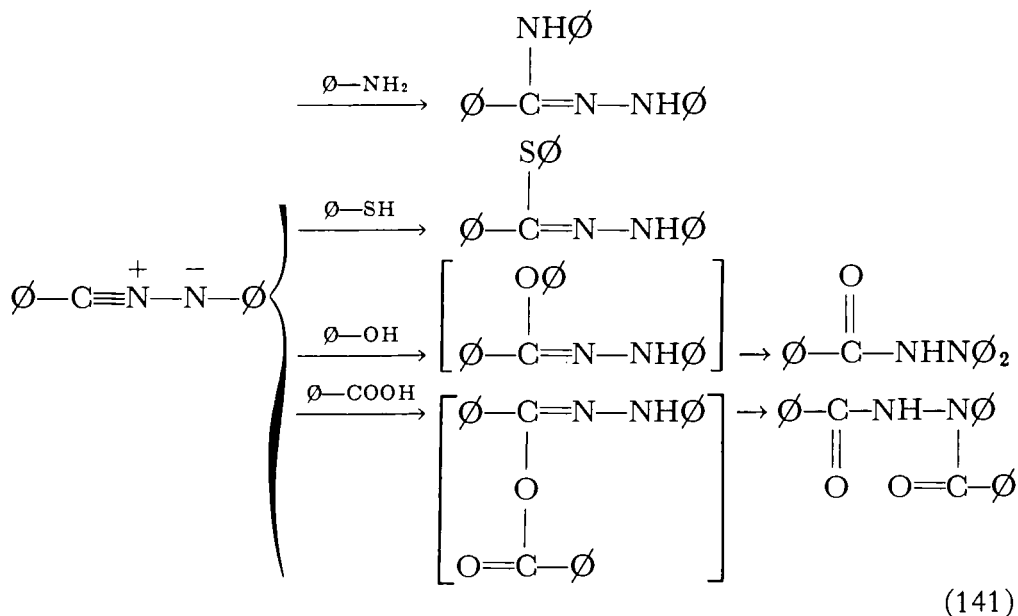
which gives a cyclic peroxide or benzophenone, is probably a result of cleavage to diphenylcarbene rather than of oxidative attack on the diazo compound.^{28b, 147}

NITRILE IMINES The reactions of nitrile imines (isodiazomethanes) are best discussed as a unit, separately from azides and diazoalkanes. Nearly all the reactions fall under the categories of addition of nucleophiles or 1,3-dipolar addition to double and triple bonds.¹⁴⁸

Isodiazomethane itself adds water readily to become formhydrazide, and easily rearranges to diazomethane, especially under catalysis by potassium hydroxide¹¹ (Eq. 140). The alkyl and aryl-substituted derivatives,

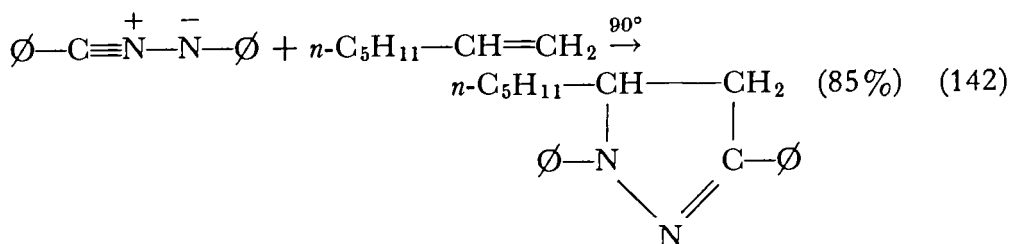


which are known only in solution, would, of course, not be expected to rearrange in this manner. The diphenyl derivative, which appears to be typical, has been the most thoroughly investigated.¹⁴⁸ Phenol, thiophenol, aniline, and benzoic acid all appear to add in the same manner, producing benzohydrazide derivatives (Eq. 141); O—to—N rearrangement, analogous to the Chapman rearrangement (Chapter 4), evidently follows in the case of the phenol and benzoic acid adducts.

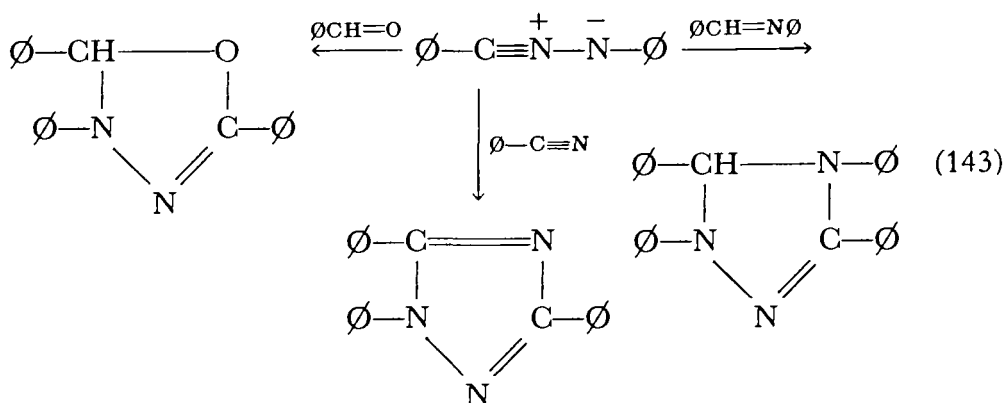


1,3-Addition occurs readily with strained olefins (e.g., bicyclopentadiene), less readily with ordinary olefins, to form pyrazolines (Eq. 142); with acetylenes, pyrazoles are produced. In the slower additions, dimerization to 1,3,4,6-tetraphenyl-1,4-dihydro-1,2,4,5-tetrazine becomes

a significant competing reaction. Benzaldehyde adds to form an oxadiazoline, and its anil adds to form a 1,2,4-triazoline (Eq. 143). Phenyl



isocyanate and isothiocyanate also undergo addition at the C=N bond.



Nitriles react to form triazoles (Eq. 143).

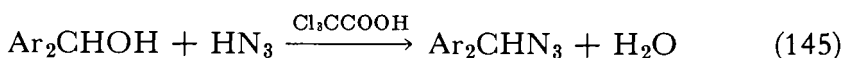
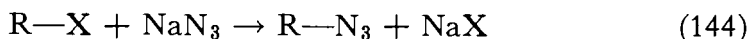
Azomethine imides, $R_2C=N^+(R)-N^--R$, undergo analogous 1,3-additions.¹⁰²

PREPARATIVE METHODS ²

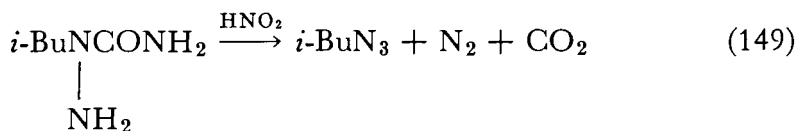
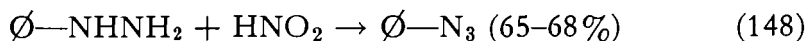
A. Azides

Alkyl azides are almost always prepared by a displacement reaction between an alkyl halide,¹⁴⁹ quaternary ammonium salt,^{43b} or toluene-sulfonate^{134, 136} and sodium or lithium azide, in refluxing aqueous alcohol, Carbitol, etc.^{149, 150} (Eq. 144). Displacement occurs with inversion.¹⁵⁰ Although it is a generally satisfactory method, there are sometimes difficulties in purification when reaction is incomplete, since azides usually boil at temperatures only slightly above or below the corresponding bromides.¹⁵¹ Silver azide has also been used.¹⁵² Tertiary alkyl azides cannot be made by bimolecular displacement, of course, owing to steric hindrance, and the few that are known have been made by variations on

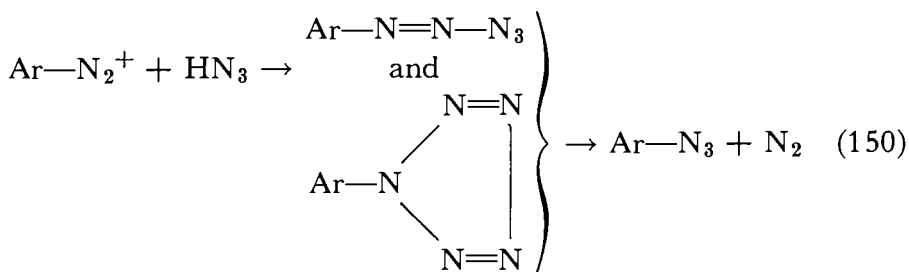
solvolysis in the presence of azide ion. Alcohols that form carbonium ions readily, such as benzhydrols and triarylcarbinols, can be converted to azides conveniently by reaction with hydrogen azide in the presence of a strong acid, such as trichloroacetic ¹⁵³ (Eq. 145). The displacement of halide with sodium azide is also a general method for acyl azides ^{31, 154} (Eq. 146).



An entirely different approach is the reaction of monosubstituted hydrazines with nitrous acid. This reaction gives azides smoothly when the substituent is acyl, ^{31, 155} or aryl ¹⁵⁶ (Eqs. 147, 148), which are base-weakening, but is usually unsuccessful with alkyl hydrazines.¹⁵⁷ This difference appears to be due to a difference in the site of nitrosation (see Chapter 9). Some alkyl hydrazines have been converted to azides through acyl derivatives in which the alkylated nitrogen is blocked ¹⁵⁸ (Eq. 149).

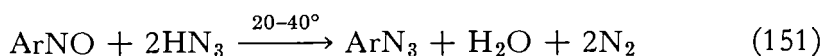


Although aryl azides are easily prepared from aryl hydrazines, it is generally more convenient to prepare diazonium salts, which react with sodium azide solution rapidly in the cold to give good yields ¹⁵⁹ (Eq. 150). The azide nitrogen is derived largely from the diazonium function, which

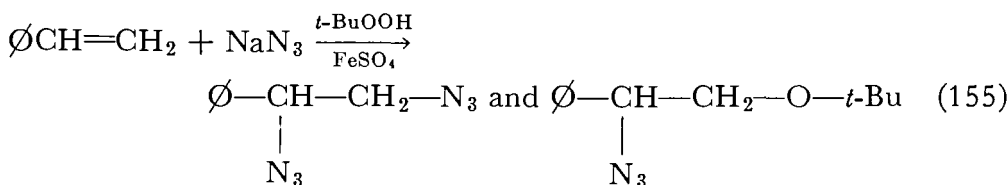
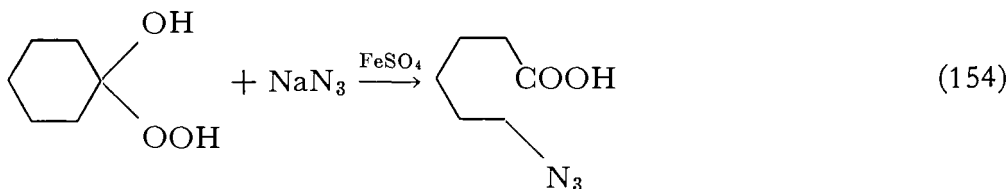
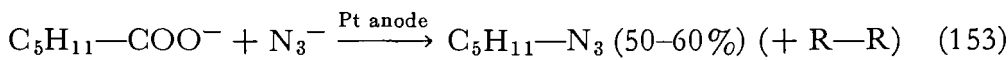
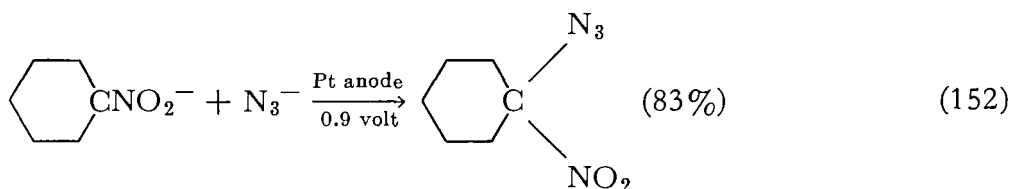


first couples to form a mixture of a diazoazide and a pentazole.¹⁶⁰ Other reagents, such as hydrazine,¹⁶¹ hydroxylamine,¹⁶² ammonia and bromine,¹⁶³ and sulfonamides,¹⁶⁴ also convert diazonium salts to azides (cf.

Chapter 11). The reaction of aryl Grignard reagents with sulfonyl azides, followed by decomposition of the resulting 1-aryl-3-sulfonyltriazene with aqueous sodium azide (Eq. 116), is a valuable alternative route when aryl halides are the only available starting material.¹¹⁴ The reaction of nitroso compounds with hydroxylamine^{165a} or with hydrogen azide^{165b} also produces azides (Eq. 151), often very smoothly, but it has seldom been employed for synthesis.



Azides have also been made electrolytically, using salts of carboxylic acids or nitroalkanes in the presence of the azide ion¹⁶⁶ (Eqs. 152, 153) and by an apparently free-radical process from hydroperoxides and olefins in the presence of ferrous ion¹⁶⁷ (Eqs. 154, 155).

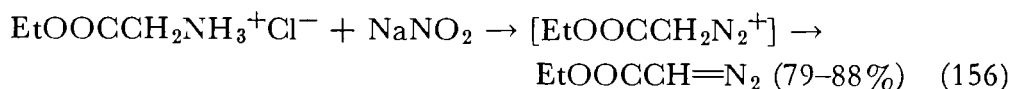


B. Diazoalkanes

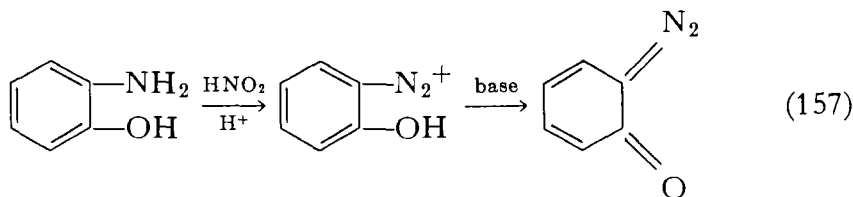
Preparative methods for diazo compounds, particularly diazomethane, are considerably more numerous than those for azides, but none of them appears to be both reliable and fully general, unfortunately. There is no analog of the simple alkylation of sodium azide, so less direct methods must be used (acylation of diazomethane is, of course, a useful procedure).

The simplest method is nitrosation of a primary amine, but it is ordinarily only successful when there are acid-strengthening groups on the α -carbon, such as carboethoxy, trifluoromethyl, etc. A diazonium ion is presumably first formed; it must expel a proton to become a diazo

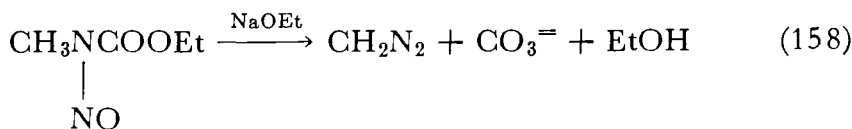
compound before other reactions involving loss of nitrogen take place. The method has been applied even to methylamine, however, by using nitrosyl chloride at -80° , and treating the resulting methylnitrosoamine with 40% KOH,^{168a} and by treating lithium methylamide with nitrosyl chloride.^{168b} The principal use of this method is in the preparation of α -diazo esters¹⁶⁹ (Eq. 156). Since the products are sensitive to acid, the preferred technique is to mix the amine hydrochloride with sodium nitrite without any additional acid; the presence of methylene chloride to extract the diazo compound as it is formed improves the yield markedly. This reaction also works in the special case of *o*- and *p*-aminophenols;



the diazonium ions obtained from them are stable, but they give up a proton on neutralization and become diazoöxides^{16, 27} (Eq. 157).

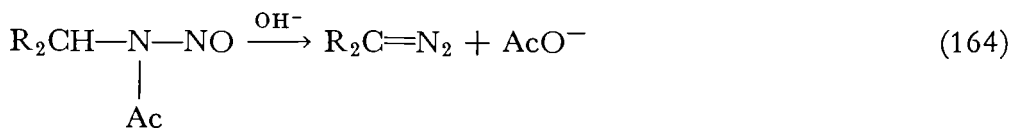
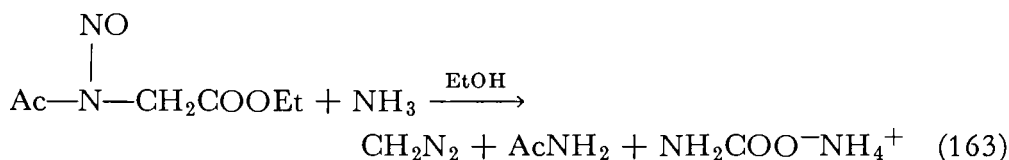
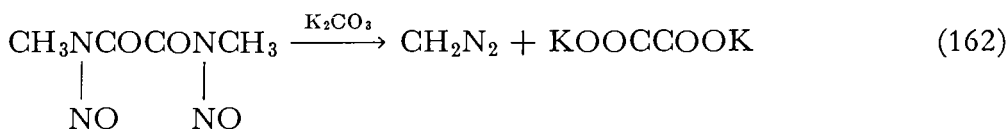
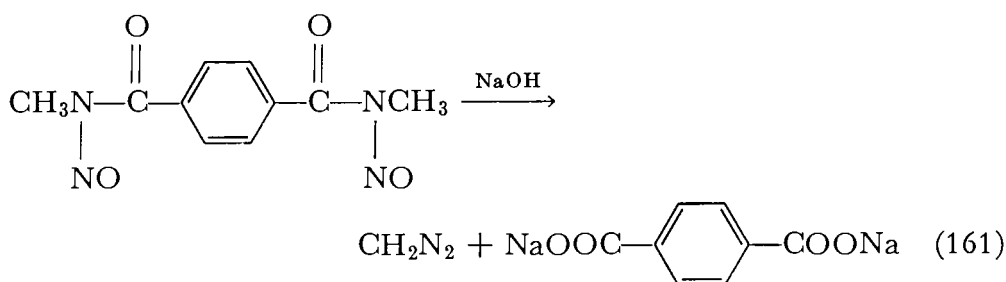
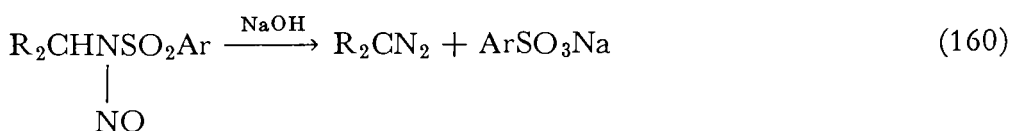
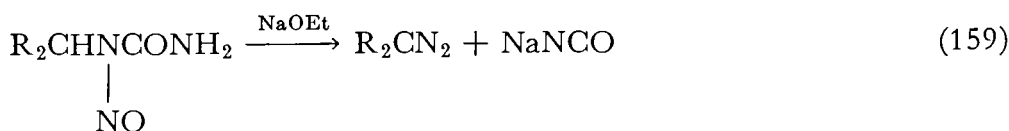


The most widely used general method for diazoalkanes is the reaction of N-alkyl-N-nitrosourethans with base^{32a, 170, 171} (Eq. 158). Alcoholic sodium or potassium hydroxides or alkoxides are required, and it is necessary to distill the diazo compound (in the presence of added ether) from the reaction mixture in order to get it free of contaminants. This feature is a severe limitation, as are the instability and highly irritating character-

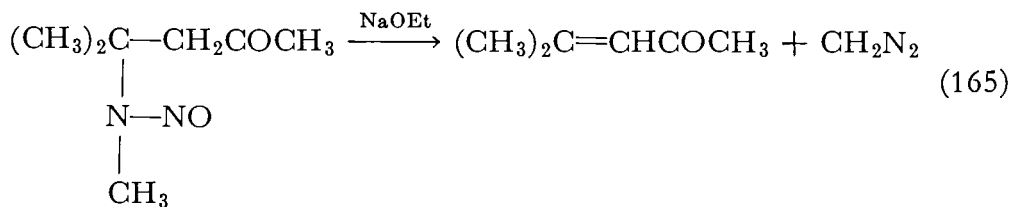


istics of the nitrosourethans (N-methyl-N-nitrosourethan is also markedly carcinogenic). In order to ameliorate these difficulties, various other types of N-alkyl-N-nitrosoamides have been used, such as N-alkyl-N-nitrosoureas,^{32a, 172} -sulfonamides,^{173, 174} -oxamides,¹⁷⁵ and -terephthalamides¹⁷⁶ (Eqs. 159–162). N-Methyl-N-nitroso-*p*-toluenesulfonamide is sold commercially as a source of diazomethane under the names “Diazald” and “Diactin,” and N,N′-dimethyl-N,N′-dinitrosoterephthalamide is sold under the name “EXR-101.” All of these sources are satisfactory for diazomethane, and N-methyl-N-nitrosourea has the special advantage that ethereal diazomethane can be prepared from it without distillation. N-Nitroso acetamides have been found useful not only for diazomethane,

but for substituted diazo compounds ^{73a, 177, 178} (Eqs. 163, 164). Chapter 15 contains further information on this subject.

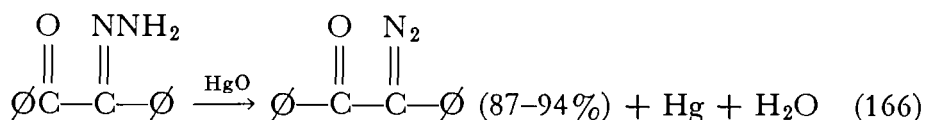


In this group also belongs the alkaline cleavage of N-methyl-N-nitroso-N'-nitroguanidine to diazomethane.^{179, 180} N-Nitroso- β -amino ketones also release diazoalkanes when treated with alkali (Eq. 165). The most simply available are those made from mesityl oxide, $(\text{CH}_3)_2\text{C}=\text{CHCOCH}_3$, by addition of a primary amine followed by nitrosation. This reaction has seen wide use as a source of diazomethane.¹⁸¹

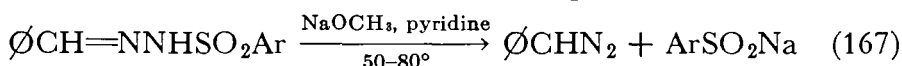


Larger diazo compounds, such as diphenyldiazomethane, are often

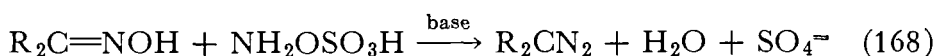
made by oxidation of hydrazones; the most commonly used oxidizing agent is mercuric oxide suspended in ether^{182, 183} (Eq. 166). A trace



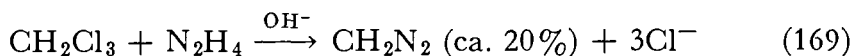
of strong alkali is usually required as a catalyst, but the reaction is even then inclined to be capricious, and different batches of mercuric oxide vary widely in activity for no obvious reason. Other oxidizing agents, notably activated manganese dioxide, are also of value. A related method involves internal oxidation, in the form of the base-catalyzed decomposition of sulfonyl hydrazones^{184, 185} (Eq. 167) (cf. Chapter 9).



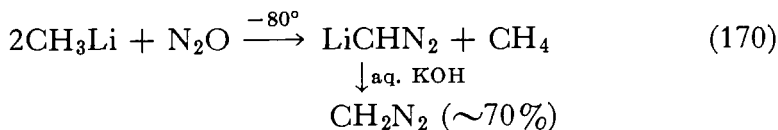
There are in addition miscellaneous other preparative methods, whose utility for the most part is limited or unexplored. The reaction of oximes with chloramine or hydroxylamine-O-sulfonic acid in the presence of base (Eq. 168), known as the Forster synthesis, has promise of considerable generality.^{185b, 186, 187} The reaction of chloroform and hydrazine in the



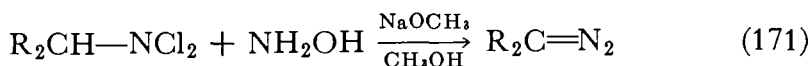
presence of alkali¹⁸⁸ (Eq. 169) is probably restricted by mechanism to



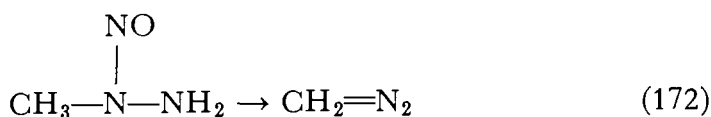
diazomethane preparation. The isomerization of isodiazomethane, in turn prepared from methyllithium and nitrous oxide¹⁸⁹ (Eq. 170), has



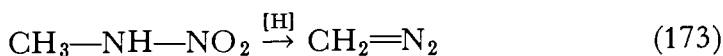
been mentioned earlier. N,N-Dichloroamines give poor yields (ca. 25%) of diazoalkanes by reaction with hydroxylamine and sodium methoxide¹⁹⁰ (Eq. 171). N-Nitroso-N-methylhydrazine has been cleaved to diazo-



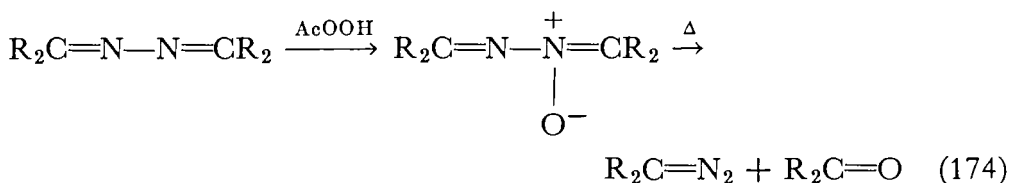
methane¹⁹¹ (Eq. 172), and methylnitramide has been reduced to



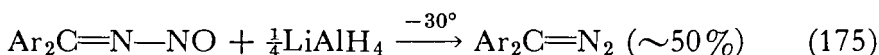
diazomethane¹⁹² (Eq. 173), but neither compound is a practical starting



material. It has been reported indirectly ¹⁹³ that N-nitroso-N-methyl-*p*-nitroaniline is cleaved by alkali to diazomethane. Cyclopentadiene (but not fluorene) is acidic enough to react with sulfonyl azides in the presence of base to provide a practical source of diazocyclopentadiene ^{115a} (cf. Eq. 117). The recently discovered azine N-oxides can be cleaved to diazoalkanes by heat, light, or traces of acid ¹⁹⁴ (Eq. 174).



The reduction of nitrosimines by lithium aluminum hydride (Eq. 175)

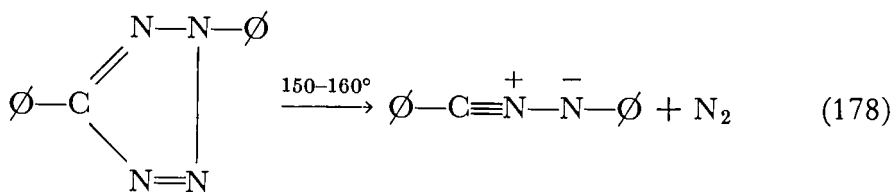
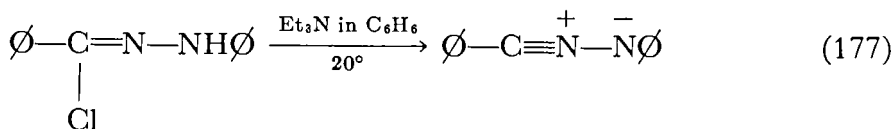
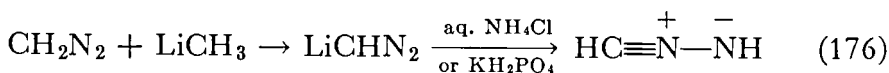


has been found to give better yields of diazo compounds, especially hindered diaryl diazomethanes, than more conventional routes.^{28b}

C. Nitrile Imines

Isodiazomethane has only been prepared from diazomethyl lithium, by cautious hydrolysis with aqueous ammonium chloride or potassium dihydrogen phosphate ^{11, 189} (Eq. 176). The method appears not to be general, for it fails even with the next homolog, isodiazaoethane,

$\text{CH}_3\text{C}\equiv\text{N}^+-\text{NH}^-$. The dehydrohalogenation of hydrazoneyl chlorides is a mild reaction of some generality, suitable for the preparation of N-substituted nitrile imines *in situ* for further reaction ¹⁴⁸ (Eq. 177). The decomposition of 1,3-disubstituted tetrazoles also gives rise to nitrile imines ^{148, 195} (Eq. 178), but the more drastic conditions required make it a less desirable method.



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chapter
eleven

Other Functions with Adjacent Unsaturated Nitrogens

(Diazonium, Azo, and Azoxy
Compounds, and Azine Oxides)

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NOMENCLATURE

Diazonium ions, $\text{Ar}-\text{N}_2^+$, are properly named by adding the suffix “-diazonium” to the name of the parent *hydrocarbon*, not the name of the aryl group. The simplest example, $\text{C}_6\text{H}_5-\text{N}_2^+$, is thus “benzenediazonium”; this additive method of constructing the names, which has had

official sanction and general use since the beginning of the century, is analogous to the use of “-carboxylic acid” as a suffix in the naming of acids. Covalent derivatives are by custom named differently when the diazo nitrogen is joined to an atom other than carbon on the one hand, or to an organic moiety on the other; cyanide derivatives also fall in the former group. The first group of compounds are named by adding the name of the attached group to “-diazo-,” as in “*p*-nitrobenzenediazocyanide,” $p\text{-O}_2\text{N}-\text{C}_6\text{H}_4-\text{N}=\text{N}-\text{CN}$; the second group constitutes the azo compounds and is taken up in a subsequent paragraph. The reason for this difference in naming is largely historical; before the general acceptance of the ionic theory, the structure of diazonium salts and their derivatives was controversial, and there was serious doubt whether the “diazo” compounds and the azo compounds were of the same structural type. The “diazo” compounds, it will be noted, are those that dissociate to some extent into diazonium ions.

It is occasionally necessary to distinguish by name the geometrical isomers that may exist. With the “diazo” group, it has long been customary to use the prefixes “*syn*-” and “*anti*-,” in analogy with oximes, rather than “*cis*-” and “*trans*-.” The preservation of this seemingly pointless distinction serves one useful purpose; as long as the stereochemistry of the diazo compounds remains at all uncertain, it allows the isomers to be designated clearly with respect to historical precedent, without committing the user to a particular geometry for the group to which a particular isomer belongs. This point will become clearer in connection with the discussion of properties.

The anion derived from the diazohydroxides, ArN_2O^- , is called the diazotate ion, and compounds of the type $\text{Ar}-\text{N}_2-\text{O}-\text{N}_2\text{Ar}$ are called diazoanhydrides, with the name of the substituent group(s) prefixed.

Azo compounds, $\text{R}-\text{N}=\text{N}-\text{R}'$, are named by three systems. When the compound is symmetrical about the azo group, it is customary to use the prefix azo before the name of the hydrocarbon, as in “azomethane,” $\text{CH}_3-\text{N}=\text{N}-\text{CH}_3$. Such a name may then serve as a stem to which the names of substituents may be attached, as in “4-nitro-3'-propylazobenzene,” $4\text{-O}_2\text{N}-\text{C}_6\text{H}_4-\text{N}=\text{N}-\text{C}_6\text{H}_4-3'\text{-Pr}$. Names such as “azoisopropane” are commonly used for their convenience, but *Chemical Abstracts* indexes such compounds according to the general I.U.P.A.C. rule for alkyl groups, by which the foregoing compound becomes “azoethane, 1,1'-dimethyl.”

A less formal nomenclature has developed for azo compounds bearing other functional groups, to avoid the rather awkward names that would arise from a rigid application of the foregoing system. Since these names are logical, unambiguous, and easily comprehensible, there seems to be no objection. Examples are “azodicarboxylic ester” or “azodi-

formic ester" for $\text{EtOOC}-\text{N}=\text{N}-\text{COOEt}$, and "azodibenzoyl" for $\text{O}_2\text{C}-\text{N}=\text{N}-\text{COO}$.

For unsymmetrical compounds, it is permissible to use such additive names as "benzeneazomethane," $\text{O}-\text{N}=\text{N}-\text{CH}_3$, or to use "arylozo-" as a prefix, as in *p*-phenylazobenzoic acid," *p*- $\text{O}-\text{N}=\text{N}-\text{C}_6\text{H}_4-\text{COOH}$. The last alternative, less commonly encountered, is to name azo compounds as substituted derivatives of the inorganic compound diimide, $\text{HN}=\text{NH}$ (sometimes also called "diazene"), as in "N-methoxy-N'-nitrodiimide," $\text{CH}_3\text{O}-\text{N}=\text{N}-\text{NO}_2$.

Formazans represent a special case; the structure $\text{R}-\text{N}=\text{N}-\text{CR}=\text{N}-\text{NR}-\text{R}$ is really a functional group by itself. The best system is to name them after the hypothetical unsubstituted parent compound, forma-

zan, $\text{HN}=\text{N}-\text{CH}=\text{N}-\text{NH}_2$. Since formazans with different substituents at the 1- and 5-positions tautomerize too easily for isomers to be distinguished, the locants C, N, N' are often used, as in "N-phenyl-C-chloro-N'-(1-naphthyl)formazan." *Chemical Abstracts* somewhat hesitantly uses the formazan nomenclature along with "azo hydrazono" substituent names that in some cases verge on the incomprehensible.

The analogous azo oximes, $\text{R}-\text{N}=\text{N}-\text{CR}=\text{NOH}$, have been called "nitrosazones," and the nitronic acids, $\text{R}-\text{N}=\text{N}-\text{CR}=\text{NO}_2\text{H}$, are known as "nitrazones."

Azoxy compounds present the special problem that the azoxy group is itself unsymmetrical, but in many azoxy compounds the position of the oxygen is unknown. The problem disappears when both substituents on the azoxy group are the same, of course, and such compounds are usually named analogously to azo compounds, by placing the prefix "azoxy" before the name of the parent hydrocarbon, as in "azoxybenzene," $\text{O}-\text{N}=\text{N}(\text{O})-\text{O}$. The *I.U.P.A.C. Tentative Rules* (1961) extend this procedure to provide names for those unsymmetrically substituted derivatives in which the position of the oxygen is not known, as in "2-phenylazoxybenzoic acid," $\text{O}-(\text{N}_2\text{O})-\text{C}_6\text{H}_4-2-\text{COOH}$, which can also be called "*o*-carboxyazoxybenzene" (but see below!). To specify the position of the oxygen, the *I.U.P.A.C. Tentative Rules* use the infixes $-\text{NNO}-$ and $-\text{ONN}-$, so that we have "2-phenyl- ONN -azoxybenzoic acid" and "2-phenyl- NNO -azoxybenzoic acid" for the isomers with the oxygen, respectively, on the nitrogen far from and near to the benzoic acid moiety. If it is necessary to number positions on both substituents, the convention is that when $-\text{ONN}-$ is used, primed numbers refer to positions on the group near the oxygen, and when $-\text{NNO}-$ is used, to positions on the group away from oxygen, as in 4'-bromo-4-nitro- NNO -azoxybenzene, $\text{Br}-\text{C}_6\text{H}_4-\text{N}=\text{N}(\text{O})-\text{C}_6\text{H}_4-\text{NO}_2$.

Two alternative ways of naming unsymmetrical azoxy compounds

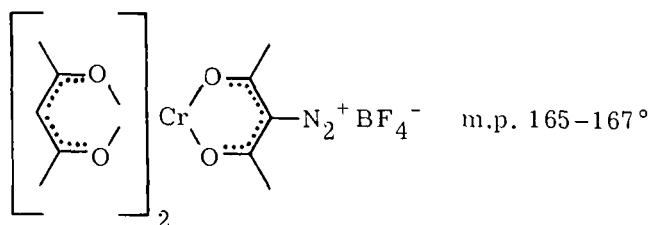
are actively used in the literature. The *Journal of the Chemical Society (London)*¹ has endorsed the device of using "arylazoxy" as a prefix, defined as the group $\text{Ar}-\text{N}=\text{N}(\text{O})-$ according to this system, the name "2-phenylazoxybenzoic acid" corresponds to the specific isomer $\text{C}_6\text{H}_5-\text{N}=\text{N}(\text{O})-\text{C}_6\text{H}_4-\text{COOH}$, and the other isomer would have the name "(2-carboxyphenylazoxy)benzene," the parentheses being used where necessary to avoid ambiguity. It is unfortunate that in some cases the same name has different meanings in this system and that of the *I.U.P.A.C. Tentative Rules*.

The other alternative is to name azoxy compounds as diimide (or diazene) N-oxides, as in "N-phenyl-N'-propyldiimide N'-oxide," $\text{C}_6\text{H}_5-\text{N}=\text{N}(\text{O})-\text{Pr}$. If this system is to be used, it would be desirable to adhere to the *Chemical Abstracts* root name "diimide," for the completely misleading root "diazine," which properly refers to a six-membered ring with two nitrogen atoms, can easily slip in by typographical error (and has, in fact, already done so in some recent papers).

Azine oxides, $\text{R}_2\text{C}=\text{N}(\text{O})-\text{N}=\text{CR}'_2$, and dioxides, $\text{R}_2\text{C}=\text{N}(\text{O})-\text{N}(\text{O})=\text{CR}_2$, have been named in the recent literature in the same way as amine oxides. The problem of specifying isomers in unsymmetrical examples, which has not yet arisen, could be handled easily by the use of N and N', as in "N-isopropylidene N'-benzylidene azine N'-oxide," $(\text{CH}_3)_2\text{C}=\text{N}-\text{N}(\text{O})=\text{CHC}_6\text{H}_5$.

PROPERTIES

Diazonium salts of the strong mineral acids are nearly colorless, water-soluble, ionic solids,² whose stability in the solid state varies from fleeting to moderate. They usually deflagrate before melting, and some, notably nitrates, detonate. Fluoroborates are somewhat less soluble than other salts and are more easily isolated. The only diazonium salts stable enough to be observed directly are those in which the diazonium group is attached to a tricoördinate carbon, which provides some stabilization by *pi*-orbital delocalization. Although most of the known diazonium salts have the diazonium group attached to a benzene or naphthalene nucleus, many other systems can sustain a diazonium ion, such as heterocyclic nuclei with aromatic character (e.g., pyridine, pyrazole, triazole) and even metal chelate systems, such as *tris*-(acetylacetonato)chromium.³

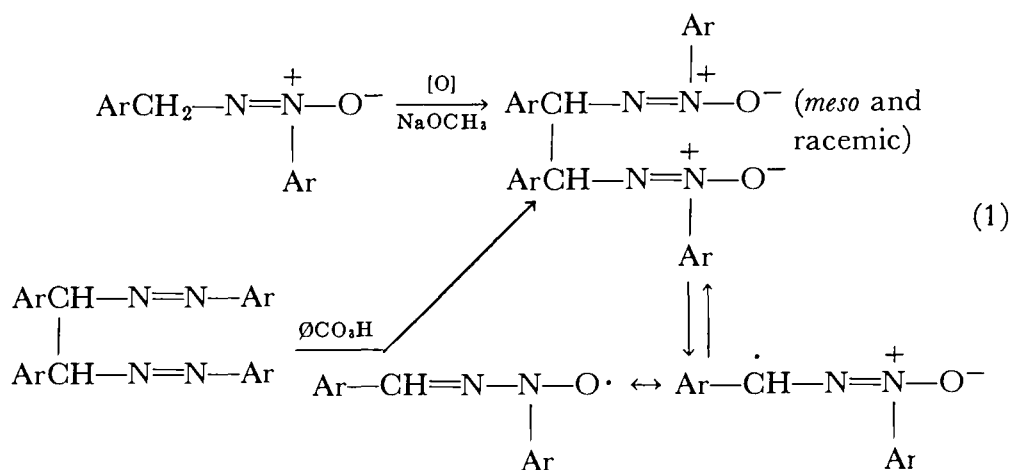


The alkali metal diazotates are water soluble, crystalline solids,^{4, 5} as is to be expected. Diazohydroxides, $\text{Ar}-\text{N}=\text{N}-\text{OH}$, have never been isolated, but their tautomers, the aryl nitrosamines, are known as very unstable solids, obtainable only at low temperatures⁴ except in the case of certain nitrosamino heterocycles.⁶ The diazoanhydrides are explosive, yellow solids that decompose slowly at room temperature if undisturbed (*bis*-(*p*-chlorophenyl) diazoanhydride has a half-life of 402 min. at 19.5°).⁷ There have been contentions that the diazoanhydrides were really nitrosotriazenes, but the unambiguous synthesis of the latter compounds, which were found to be quite different, has resolved the question.^{7b}

Azo compounds of the azoalkane and azobenzene type are in general much more stable than the diazonium compounds and their derivatives. The aliphatic members are gases or volatile, light yellow liquids, having an unpleasant, sweetish odor, such as *trans*-azomethane, mp -78° , bp 2° , and 2,2'-azopropane, bp 88° . Azomethane is appreciably soluble in water. Azobenzene exists as a *trans*-isomer, an orange-yellow solid of mp 68° , and a less stable *cis*-isomer, mp 71° ; the difference in melting point between geometrical isomers is usually larger, however, as in *p,p'*-azotoluene, mp 70° (*trans*) and 37° (*cis*). The monosubstituted compound, phenyldiimide, has apparently been observed in solution at -60° as an extremely unstable substance.⁸

Azoxy compounds are in general less volatile and of paler color than their azo partners. The simple aliphatic members, such as azoxymethane, bp 98° , are colorless liquids; azoxymethane is miscible with water, but 2,2'-azoxypropane is insoluble.^{9a} α,α' -Azoxytoluene^{9b} is a solid, mp $42-43^\circ$. The aromatic members are also solids, and many have been isolated in two geometrically isomeric forms. Azoxybenzene, for example, is commonly encountered in a light yellow form, mp 36° , believed to be *trans*, and a colorless form, mp 86° , believed to be *cis*. The lower melting *trans* forms appear in general to be the more stable forms of azoxybenzenes. High-melting, insoluble substances that were once believed to be the *cis* isomers of benzylic azoxy compounds have since been recognized as oxidative dimers¹⁰; they can be synthesized from *bis*-azo compounds, and nuclear magnetic resonance integration reveals too few hydrogens for the monomeric structure (Eq. 1). These *bis*-azoxy compounds have the interesting characteristic of dissociating reversibly into free radicals.¹⁰

Thio analogs of azoxybenzenes have been reported, but later evidence has convincingly identified them as the isomeric sulfur diimides, $\text{RN}=\text{S}=\text{NR}$.¹¹ Hydroxyazoxy compounds, $\text{R}-\text{N}(\text{O})=\text{NOH}$ and $\text{R}-\text{N}=\text{N}(\text{O})\text{OH}$, are tautomeric forms of nitrosohydroxylamines and nitramides, respectively; they and their alkyl and acyl derivatives are discussed more thoroughly in Chapter 15. Hyponitrite esters, $\text{RO}-\text{N}=\text{N}-\text{OR}$, are also discussed there. Fluoroazoxy compounds, such as $\text{O}-\text{N}(\text{O})=$



N—F, bp 78°/4 mm., are known in small number ¹²; they are very stable and appear in general to be liquids. The few azine monoxides ^{13a} and dioxides ^{13b} that have been reported are reasonably stable, colorless solids.

The acid-base characteristics of diazonium compounds and their derivatives are relatively complex and will be discussed after first dealing with those of the azo and azoxy compounds. Both of these latter classes are devoid of acidic properties in water solution. The group R—N=N=N(O)— is evidently electron-withdrawing, for it retards aromatic substitution ¹⁴ and would be expected to be more effective in stabilizing an α -carbanion than the isomeric group, R—N(O)=N—, which is *ortho-para* directing,^{1, 14} and does not retard substitution. The susceptibility of azoxymethane to destruction by hot, concentrated sodium hydroxide ^{9a} argues for at least threshold acidity in aliphatic azoxy compounds, perhaps associated with the hydrogens adjacent to the oxidized nitrogen.

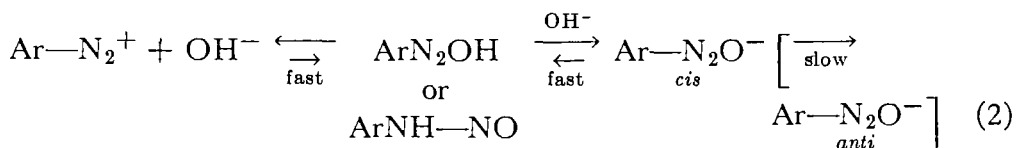
The basicity of azo compounds is so low that protonation is not observed in aqueous solution except when other groups in conjugation markedly modify the nature of the system. The situation then becomes part of the involved subject of acid-base indicators, of which methyl orange is a familiar example. The base strengths of aliphatic azo compounds have not been measured, owing to the rapid isomerization to hydrazones brought about by strong acids, but *trans*-azobenzene, $\text{pK}_a -2.95$, and its *cis* isomer, $\text{pK}_a -2.25$, are weaker bases than water.¹⁵ Salt-like addition compounds with strong acids have nevertheless been isolated. The subject of the site of protonation has been a source of controversy, the question of debate being whether the proton is linked to a particular nitrogen or is bound symmetrically to the pi-electrons of the double bond ^{15, 16}; the existence of distinct conjugate acids from *trans* and *cis* azobenzenes is difficult to reconcile with *pi*-bond protonation,

however. Ternary diazenium salts, having the ion $\text{Ar—N}=\text{N}^+\text{Ar}'_2$, are

also known, in which Ar is a 3-pyrazolyl group.¹⁷ Azoxy compounds are even more weakly basic, the difference being similar to that obtaining between a tertiary amine and its N-oxide; azoxybenzene^{18a} has $pK_a -5.15$, and substituted derivatives have values between -5.47 and -9.83 (in aqueous alcohol).^{18b} Protonation is believed to take place on the oxygen.

Azine oxides are not obviously basic, but the monoxides are sensitive to acids.

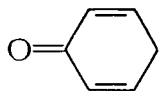
Diazonium salts of the strong mineral acids are neutral in water solution, from which we may conclude that the hypothetical diazohydroxides, $Ar-N=N-OH$, are highly dissociated. The diazonium ion is thus only a very weak acid. When a diazonium salt is made strongly basic, diazohydroxides are not formed in significant amounts, but instead, the diazonium salt consumes two equivalents of hydroxide ion to form the diazotate ion (Eq. 2), whose salts can be isolated with sufficient care.⁵



The pH of solutions of diazotate salts, 7 to 12, indicates that the parent acids are weak to fairly strong. We thus have the phenomenon of a dibasic acid (ArN_2^+) whose first acidity constant is very much smaller than its second.¹⁹⁻²¹ This, of course, is the opposite of all common experience and was for decades a cause of confusion in the interpretation of diazonium reactions. The unusual state of affairs is possible because the two successive acidic species are of different types, the first being a Lewis acid, the second a Brønsted acid. It has been estimated that not more than 1% of diazohydroxide is present at equilibrium; when a diazonium salt is treated with one equivalent of base, half of the diazonium ion is converted to diazotate, and half remains as such. The potentiometric titration curve for the addition of two equivalents of hydroxide to one of diazonium salt shows only one inflection, and from it can be obtained only $pK_{app} = pK_1 + pK_2/2$, not pK_1 or pK_2 by themselves.²⁰ For unsubstituted benzenediazonium ion, the apparent constant $pK_{app} = 11.9$, for the *p*-nitro derivative, 9.44, and for *p*-methyl, 12.59.¹⁹ The Hammett regression constant ρ is thus unusually large ($+6.3$).¹⁹ The investigation of the acid-base relationships among diazonium derivatives is further complicated by isomerism among the diazotates and presumably the diazohydroxides; the initially formed *syn* diazotates isomerize to the *anti* forms, usually slowly, but in some cases rapidly. The acidity of *anti*-benzenediazohydroxide (*not* the isomer in rapid equilibrium with the

diazonium ion) has been separately estimated ²² as $K = 7.2 \times 10^{-7}$ at 20°.

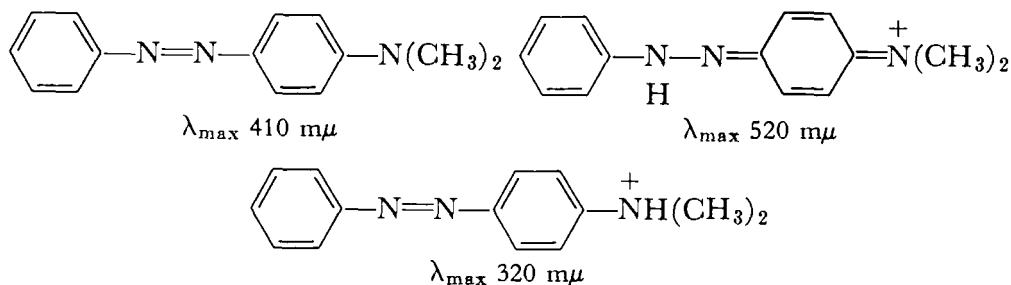
The infrared spectrum of diazonium salts shows an absorption band near 2260–2300 cm^{-1} , clearly due to triple bond stretching.^{23, 24} Such a band is not found in covalent diazo compounds, azo compounds, or azoxy compounds. Benzenediazocyanide, for example, shows only the nitrile absorption in the triple-bond region, and *p*-chlorobenzenediazoanhydride has no absorption between 1500 and 2800 cm^{-1} .²⁵ Absorption assignable to $\text{N}=\text{N}$ stretching is absent or very weak in most diazo and azo compounds, an expected consequence of the symmetry of the bond; such absorption has been identified variously with bands between 1460 and 1550 cm^{-1} .^{4, 26–28} In azoxy compounds, such absorption is more prominent, and has been observed in the region 1495–1530 cm^{-1} (a band at 1285–1344 cm^{-1} , attributed to $\text{N}-\text{O}$ stretching, is also characteristic of azoxy compounds).^{9, 10, 29} The diazo oxides show absorption at 2070–2080 cm^{-1} , which is lower than would be expected for a diazonium structure, but is consistent with a diazoalkane structure,



$\text{O}=\text{C}_6\text{H}_4=\text{N}_2$; the appearance of carbonyl absorption near 1600 cm^{-1} , similar to that of open-chain α -diazoketones, confirms the identification of the diazo oxides as diazoalkane derivatives rather than inner-salt diazonium derivatives.³⁰ *Ortho*-diazooxides are similar, but their sulfur analogs are transparent in the 2000 cm^{-1} region, and must be considered as benzothiadiazoles.³¹

The electronic spectra of azo compounds are of dominating importance because of the widespread use of azo compounds as dyes and indicators. The extensive literature on the involved subject of color and constitution has been reviewed elsewhere,³² and will not be taken up here. Aliphatic azo compounds have a weak yellow color that results from end absorption of a low-intensity band in the near ultraviolet in the region 340–380 $\text{m}\mu$, believed to be due to an $n \rightarrow \pi^*$ transition ^{27, 28, 32, 33}; this band may appear as an inflection or shoulder on a stronger band farther from the visible. Conjugation with one or two benzene rings introduces the possibility of strong bands due to $\pi \rightarrow \pi^*$ transitions as well, but these do not appear in the visible range unless auxochromic groups, such as amino or hydroxyl, are also present in *ortho* or *para* positions. It is the resulting shift of this band into the visible region that is responsible for the deep color of the azo dyes (the color of azobenzene itself results from the weak $n \rightarrow \pi^*$ absorption at 443 $\text{m}\mu$; the $\pi \rightarrow \pi^*$ absorption is at 319 $\text{m}\mu$). Since the absorption maximum is sensitive to the electronic character of substituents, it is easily affected by protonation or deprotonation of the common auxochromic groups; this phenomenon is respon-

sible for the indicator properties of such compounds as methyl orange. In a simple, representative case, *p*-dimethylaminoazobenzene, the conjugate acid is of redder color. The evidence suggests that protonation occurs in part on the amino group, in part on the azo group, but the matter is still controversial.³⁴ It is significant, however, that even in azo-



benzene itself, the $\pi \rightarrow \pi^*$ transition is shifted toward the visible,³³ and the conjugate acid is deep red.

The ultraviolet spectra of azoxy compounds are usually extremely similar to those of the corresponding azo compounds. The aliphatic members have a band at 217–223 $m\mu$ with a shoulder at 273–287 $m\mu$ ¹; azoxybenzenes differ from the azobenzenes principally by the lack of the weak $n \rightarrow \pi^*$ band in the 440–470 $m\mu$ region, wherefore their weaker color.^{10, 35}

The diazonium ion function is strongly electron-withdrawing, as will be seen in the nature of some of the reactions of diazonium salts. *p*-Chlorobenzenediazonium fluoborate shows NMR signals at 0.94 and 1.50 τ , considerably downfield of the corresponding potassium diazotates, which give signals at 2.26 and 2.74 τ (*syn*-isomer) or 2.17 and 2.26 τ (*anti*).³⁶ This effect manifests itself, *inter alia*, in the high acid strength of the *p*-substituted phenol³⁷ (*p*-hydroxybenzenediazonium ion), pK_a 3.40, about 10^6 times that of phenol itself; the Hammett substituent constant σ_p has been estimated to be between 1.5 and 3, σ_m 1.7. The azo group, by contrast, is apparently *ortho-para* directing toward electrophilic substitution, and only when it is protonated does it strongly activate a benzene ring toward nucleophilic attack.³⁸ Azobenzene shows multiplets in the NMR spectrum centered at 2.1 and 2.55 τ (chloroform solution).

The azoxy grouping is clearly electron-withdrawing toward groups attached to the oxygenated nitrogen, but has little effect on groups attached to the bare nitrogen. Not only are azoxybenzenes attacked on the ring away from oxygen by electrophilic reagents,^{1, 14} but hydrogens α to the oxygenated nitrogen in aliphatic azoxy compounds give an NMR signal considerably downfield of the other α -hydrogens and

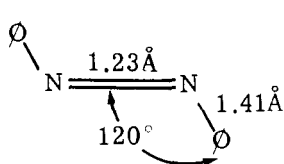
of the corresponding azo compounds.^{9b} The group $\text{RN}=\text{N}(\text{O})-$ can be regarded as an isostere of the nitro group and can be written as

$\text{RN}-\overset{-}{\text{N}}\overset{+}{\text{N}}(\text{=O})-$ as well as the conventional way. Indeed, the $\text{N}-\text{O}$ stretching frequency, $1256\text{--}1282\text{ cm}^{-1}$, is considerably higher than that for ordinary semipolar bonds and corresponds to a bond order near $1\frac{1}{2}$. Linnett and Rosenberg³⁹ have proposed representing azoxy compounds by a structure with three-electron bonds, for which is claimed reduced interelectron repulsion.

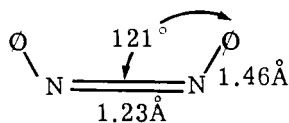
The structure of diazonium, azo, and azoxy compounds was an area of major controversy for decades, but most of the questions have been resolved as more powerful physical methods became available. Most of the questions center about isomerism. Diazonium salts have not been observed in isomeric forms, but diazotates, numerous diazo and azo compounds, and azoxy compounds are known in two forms. As has been implied in the discussion thus far, these forms are generally believed to be a consequence of geometrical isomerism about the $\text{N}=\text{N}$ double bond. The historical development of the evidence has been reviewed in detail elsewhere⁴⁰ and will be only briefly surveyed here.

Diazo compounds and the diazotates when first formed from diazonium salts are usually in a less stable, reactive form, that more or less slowly changes to a less reactive, isomeric form. By analogy with olefins and oximes, the less stable forms were assigned the *syn-* (*cis*) configuration. The two forms are completely distinct in solution as well as in the solid state. Differences in electronic absorption spectra, dipole moments, and other physical properties are consistently parallel among a wide variety of diazotates,^{41, 42} diazocyanides,²⁵ diazosulfonates,⁴³ and especially significantly, azobenzenes. From the large amount of accumulated data, it seems inescapable that the existence of pairs of isomers is in all cases due to the same cause.

The existence of geometrical isomers is on the firmest footing in the case of azobenzene, where both forms have been investigated by X-ray diffraction.⁴⁴ The stable form, definitely shown to be *trans*, is converted



trans, m.p. 68°
dipole moment⁴⁵ 0 D.

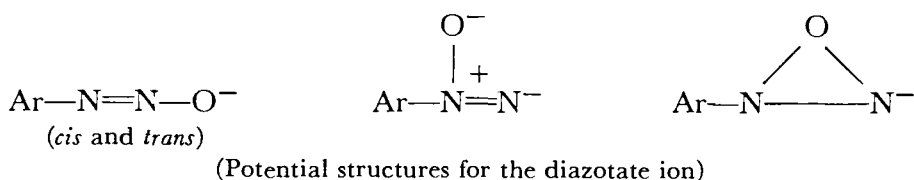


cis, m.p. 71°
dipole moment⁴⁵ 3.0 D.

by irradiation into the *cis* form, which slowly reverts back in the dark.

Azomethane has been investigated by electron diffraction ⁴⁶; it has the *trans* structure, with angles and interatomic distances comparable to those of azobenzene.

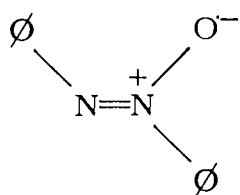
In view of the far-reaching, close analogy between the isomers of azobenzene and those of the diazo compounds, the argument by analogy that their structures are similar is generally accepted. Only in the case of the diazotates has this conclusion been seriously disputed in recent years. Three structurally isomeric forms can, in fact, be written; the evidence for geometrical isomerism, which has been critically reviewed, ⁴⁷



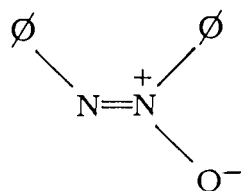
is somewhat less convincing than it once was, as a result of the discovery of the easy interconversion of nitrones and oxaziridines. It had been argued that diazotate isomers must be geometrical because of their easy interconversion, it being held that oxygen migration would be a difficult process. The possibility that interconversion could take place through phenyl migration has been disproved by nitrogen isotope labeling experiments. ⁴⁸

The azoxy compounds were for a long time considered to be oxadiaziridines, thus having a symmetrically placed oxygen. Demonstration of the existence of structural isomers ⁴⁹ led necessarily to the unsymmetrical, open-chain structure accepted today. Confirmatory evidence has continued to accumulate, until there is no longer any doubt. Apart from essentially physical evidence, compounds of the type $p\text{-RR}'\text{R}''\text{C}-\text{C}_6\text{H}_4-\text{N}(\text{O})=\text{N}-\text{C}_6\text{H}_4-p\text{-CRR}'\text{R}''$ have been shown to exist in two resolvable pairs of racemates ⁵⁰; the symmetrical azoxy structure would have resulted in one racemate and a *meso* form.

Azoxybenzene, which is incapable of structural isomerism of the foregoing type arising from the site of attachment of the oxygen, was nevertheless early discovered to exist in two isomeric forms. These might reasonably be open-chain and cyclic forms, or geometrical isomers of the open-chain form, which would be expected to result from restricted rotation about an $\text{N}=\text{N}$ bond. The similarity of the infrared absorption spectra indicates that the structures are very similar, being inconsistent with a cyclic form; the differences in ultraviolet spectra are consistent with geometrical isomerism. ⁵¹ Which isomer is which is established by the dipole moments ⁵¹ and by the preparation of one isomer by oxida-

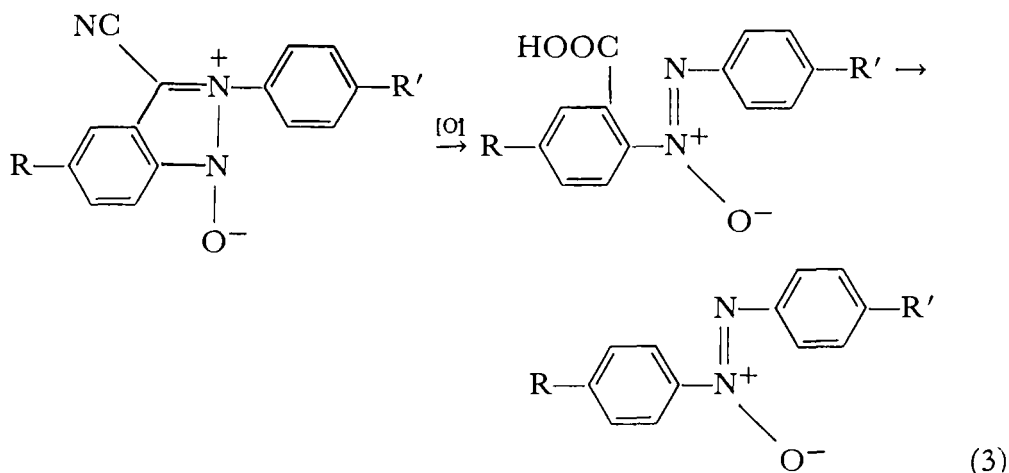


trans, stable,
mp 36°, light yellow,
easily soluble, dipole
moment 1.70 D.

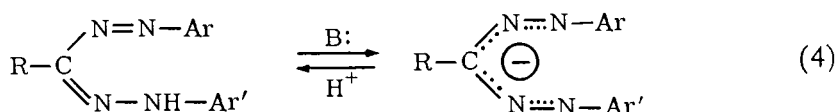


cis, labile,
mp 86°, colorless,
low solubility,
dipole moment 4.67 D.

tion of known *trans*-azobenzene, the other from *cis*-azobenzene.^{35, 52} Further support is found in the preparation of *trans*-azoxybenzenes by ring opening of indazole oxides,⁵³ a process that also establishes the identity of the structural isomers (Eq. 3).



The formazans⁵⁴ (α -hydrazono azo compounds) behave as members of a class distinct from either simple azo compounds or hydrazones, and the formazyl group may properly be considered as a unit functional group. Most of the known representatives bear aryl groups on nitrogen and are deeply colored. The formazan function is very weakly basic, and salts are hydrolyzed by dilution. The anion is symmetrical about the central carbon, similar to carboxylate anions (Eq. 4), and it is thus not surprising that formazans should be acidic enough to form salts with strong alkalies.



Nitrosazones and nitrazones are in general crystalline solids with a distinct acidic character.⁵⁵ N-Phenylnitrosazone (phenylazoformaldoxime, $\text{C}_6\text{H}_5\text{—N=N—CH=NOH}$) is a yellow solid, mp 94°; N-phenylnitra-

zone, $\text{O}=\text{N}=\text{N}-\text{CH}=\text{NO}_2\text{H}$, exists in two modifications (α , mp 75° ; β , mp 85°), which may perhaps be geometrical isomers.

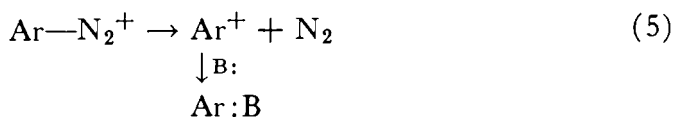
The discovery of exotic and unstable structural types in nature continues to yield surprises. Even a diazonium salt, $p\text{-HOCH}_2\text{C}_6\text{H}_4\text{—N}_2^+$, has been identified; it is formed by enzymatic oxidation of the corresponding hydrazine in the stem of the familiar and delectable mushroom.⁵⁶ The discovery of macrozamin, an azoxy compound obtained from an Australian fern,⁹ has greatly stimulated investigations in the field of aliphatic azoxy compounds.

REACTIONS

A. Diazonium Salts⁵⁷

The reactions of diazonium salts can be conveniently classified into: solvolysis reactions, in which the diazonium function is lost as nitrogen and replaced by hydroxyl or alkoxyl; coupling with nucleophiles, by which diazo or azo compounds are produced; C-arylation reactions, in which aryl radicals and/or aryl cations may be involved, with or without catalysis; a large group of replacement reactions, catalyzed and uncatalyzed, closely related to the C-arylation ones; and oxidation-reduction reactions. This classification is necessarily somewhat arbitrary, but has the advantage of being essentially operational rather than mechanistic. Mechanistic classification has also been used, particularly with respect to homolytic versus ionic reactions, but has usually foundered on the ambiguity of the mechanistic evidence on the one hand, and the fact that some reactions appear to go by both homolytic and ionic paths. Another small group of reactions not involving the diazonium function directly also deserves mention here; these are the reactions induced elsewhere on a benzene ring by the powerful electron-withdrawing character of the diazonium function.

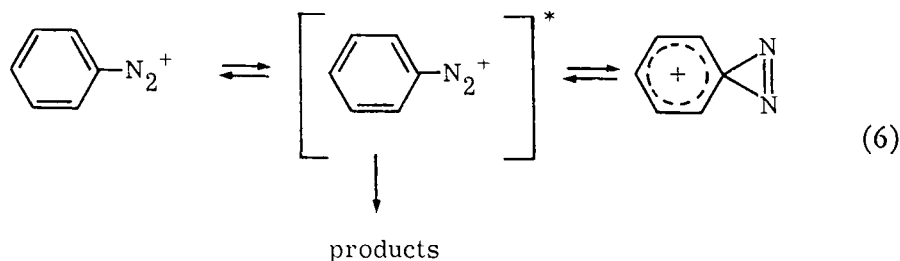
SOLVOLYTIC REACTIONS The benzenediazonium ion is susceptible to attack by nucleophiles at either the outer nitrogen or at the 1-carbon. Strong nucleophiles generally couple at the nitrogen atom to give isolable products, but weak nucleophiles, such as water or chloride ion, show little or no reactivity toward diazonium salts until conditions are reached where the salt is actively decomposing independent of attack by such nucleophiles. In the simplest cases, this might be loss of nitrogen as a result of thermal collisions, forming an aryl cation, which reacts avidly and with little selectivity with nucleophilic species in the medium⁵⁷ (Eq. 5). This view is supported by the fact that the decomposition of



diazonium salts in acidic aqueous solution is first order, and the rate is quite independent of the presence of many anions.⁵⁸ The inferred intermediates are evidently very reactive and unselective, so that in water solution, phenol formation is bound to predominate. The rate constants for reaction with water and with chloride ion have actually been determined to have the ratio 2.5 at 100° by comparing the ratio ArOH/ArCl in the products with the composition of the medium.⁵⁹ It is evidently this lack of selectivity that defeats the attempt to replace the diazonium moiety by many of the common anions by uncatalyzed decomposition in aqueous solution.

The solvolysis of diazonium salts cannot actually be as simple a process as the above presentation implies, however, for there are some more or less enigmatic observations that cannot be accounted for by it. One of them is that some anions, particularly thiocyanate and bromide, accelerate the solvolysis. The acceleration caused by bromide is accompanied by an increase in the proportion of ArBr in the product, from which it is reasonable to conclude that a bimolecular reaction between ArN_2^+ and Br^- is also involved.⁶⁰ Against this stands the observation that the ratio ArOH/ArBr in the product is independent of pressure when the decomposition of $p\text{-O}_2\text{NC}_6\text{H}_4\text{N}_2^+$ in aqueous bromide solutions is studied up to very high pressures.⁶¹ More unsettling than these observations is the discovery that when a diazonium salt labeled isotopically at one nitrogen is partially decomposed, the remaining portion shows a considerable amount of isotope scrambling, indicating a partial turnaround of the diazonium moiety in some manner.^{62, 63} A diazonium salt that has not been allowed to decompose in part does not show scrambling.

The foregoing observations and the fact that the acceleration by thiocyanate ion is greater than the concurrent isotope scrambling has led to the proposal^{62, 63} that there may actually be two discrete intermediates preceding product formation and that each of these may revert to ArN_2^+ . The first intermediate, which cannot give rise to turnaround, has been suggested to be an excited state of ArN_2^+ (Eq. 6); the second state may be a spirodiazirine, in which the nitrogens are structurally equivalent. It is not necessary to invoke the intermediate formation of Ar^+ . The



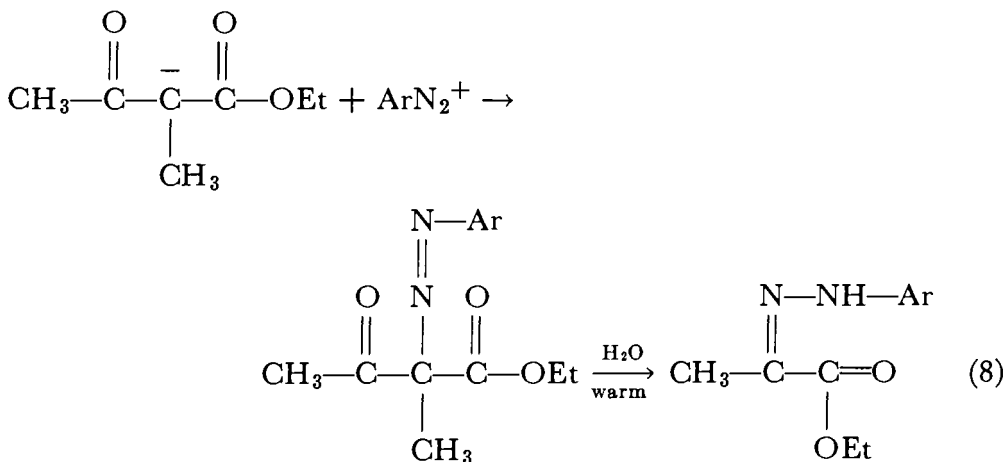
isolation of diazirine itself ("cyclodiazomethane") lends credence to this proposal (see Chapter 10).

COUPLING The well-known reaction called coupling consists of the union of a nucleophile with the outer diazonium nitrogen, producing an azo compound (Eq. 7). Probably all such reactions are reversible, although many of them are so far to the right at equilibrium that they are

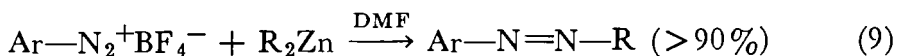


for practical purposes irreversible. With some nucleophiles, the initial product appears to be of the *syn* configuration, but slowly isomerizes to the more stable *anti* form; with others, no evidence for an intermediate *syn* form has been obtained.

COUPLING TO CARBON The most important coupling reactions are those to carbon, nitrogen, or sulfur; coupling to oxygen is unusual and gives easily dissociated products. The simplest form of coupling to carbon is probably with cyanide ion, which gives first orange *syn*-diazocyanides, which rearrange to the somewhat redder *anti* isomers.^{42, 64} Coupling also occurs with other carbanions, especially those derived from β -diketones.⁶⁵ The initially formed azo compounds are very easily



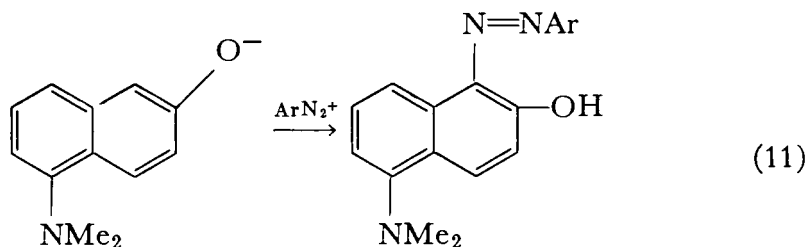
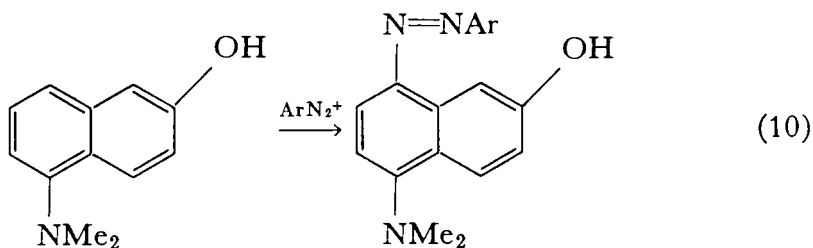
converted to hydrazones, accompanied if necessary by solvolytic removal of one of the acyl groups^{66b} (Eq. 8). The overall process is known as the Japp-Klingemann synthesis. The potential carbanions of organometallic compounds also couple when dry diazonium salts are used^{66a} (Eq. 9). Coupling is in some instances observably reversible.^{66b,c} Termini-



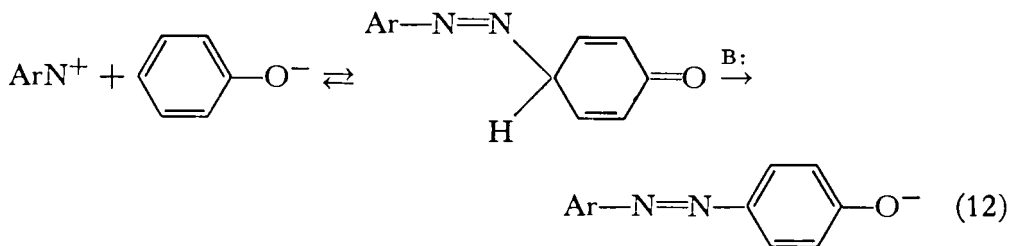
nal acetylenes couple to form hydrazones of α -ketoaldehydes.⁶⁷

Coupling to carbon may also be accomplished by electrophilic attack

on benzene rings suitably activated by hydroxy or amino groups and leads to substituted azobenzenes. Because of the great importance of this reaction in the dye industry, it has been intensively investigated.⁶⁸ Diazonium salts bearing electron-withdrawing substituents, such as nitro, are understandably the most strongly nucleophilic and couple the most rapidly.⁶⁹ Phenols (and naphthols) react only as the anions,⁷⁰ in which the ring is more strongly activated, whereas dialkylanilines couple in the form of the free bases. As a consequence, it is possible to control the site of coupling with an amino naphthol by proper selection of the pH of the medium (Eqs. 10, 11).



Studies of the kinetics of coupling to phenols and anilines and their naphthalene analogs have revealed that the initial step is a reversible bond formation between the diazonium nitrogen and a ring carbon, followed by a base-assisted departure of the proton on that carbon (Eq. 12). The first step is commonly rate determining, and there is then no kinetic isotope effect when hydrogen at the site of substitution is replaced by

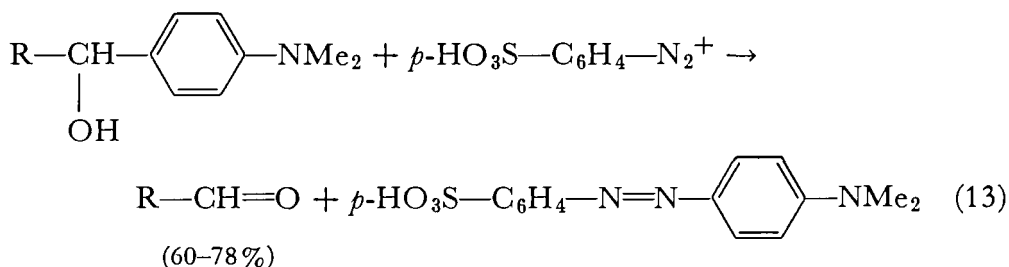


deuterium. The rate-determining step is easily shifted to the proton-removal reaction by suitable substitution, however, and isotope effects with a value of k_H/k_D as high as 6.4 have been observed.⁷¹

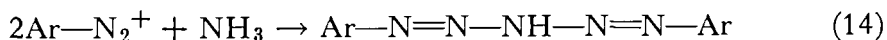
The question of the site taken by the entering azo group is of great technical importance, since *o*-hydroxy azobenzenes are weaker acids

(owing to chelate hydrogen bonding) than their *para* isomers, and are thus less susceptible to color alteration from contact with bases. *Para* substitution usually predominates overwhelmingly with benzene derivatives, but coupling to naphthalene derivatives is sensitive both to the nature of the diazonium compound and to the reaction conditions and may be made to occur predominantly *ortho* to an activating hydroxyl in an α position.⁶⁸ These effects have been attributed to the incursion of species other than ArN_2^+ as the attacking agent and to the steric requirements of the base required to remove the proton from the carbon attacked by the diazonium ion. Multiple coupling to produce *bis*- and *tris*-azo compounds has been observed.

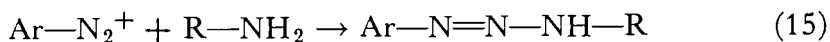
The preference for *para* coupling with benzene derivatives is so great that the entering diazonium moiety will even displace another substituent already present if it can be ejected as a cation of not too high energy. *p*-Dimethylaminobenzyl carbinols, for example, are cleaved in good yields by diazonium salts to aldehydes and *p*-dimethylaminoazobenzenes⁷² (Eq. 13).



COUPLING TO NITROGEN Diazonium salts couple with all manner of nitrogen compounds having an N-attached hydrogen. The initial coupling products are in general stable and isolable except when α -elimination can occur, in which case an aryl azide is likely to be formed (many examples of such behavior are listed in the preparative section of Chapter 10). Ammonia couples with two equivalents of diazonium ion to form pentazadienes^{73a} (Eq. 14), and only rarely have aryl triazenes, $\text{Ar}-\text{N}=\text{N}-\text{NH}_2$, been isolated.^{73b} Primary amines, both aliphatic and aromatic,

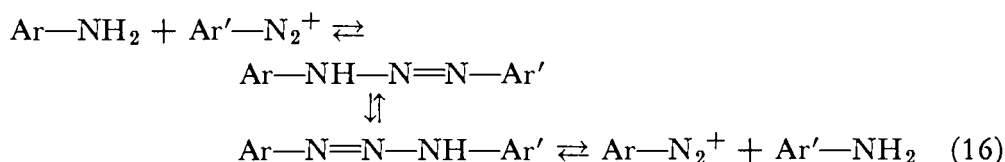


are also easily coupled with diazonium salts. The triazenes produced (Eq. 15), often called diazoamino compounds, do not couple further when

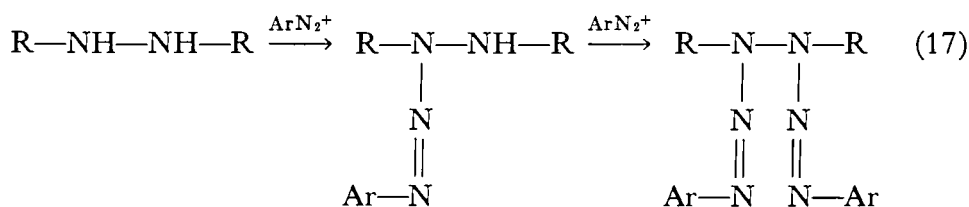


derived from anilines, but with aliphatic amines, coupling occurs so readily to give pentazadienes that it is difficult to isolate the triazenes. With secondary amines, coupling is obviously limited to triazene formation. Coupling to the nitrogen of aromatic amines must, of course,

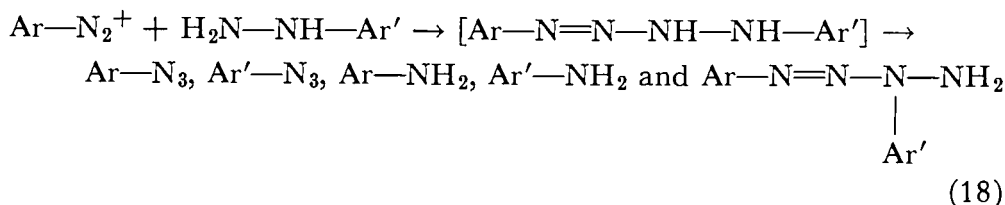
compete with coupling to a ring carbon. Since coupling to nitrogen is reversible, especially in acid solution, diaryltriazenes are more or less easily isomerized to aminoazobenzenes, the products of ring coupling.⁷⁴ Furthermore, since triazenes with two different aryl groups equilibrate readily with their tautomers, another consequence of reversibility of coupling to nitrogen is diazonium-amine interchange (Eq. 16), which can occur in acid solution. It has been demonstrated by isotopic labeling that the alternative possibility, reversible diazotization, is not involved.⁷⁵



Hydrazine derivatives may couple with one or two equivalents of diazonium salt; in the latter case, coupling preferentially occurs at separate nitrogens⁷⁶ (Eq. 17). Unless each nitrogen on the hydrazine derivative

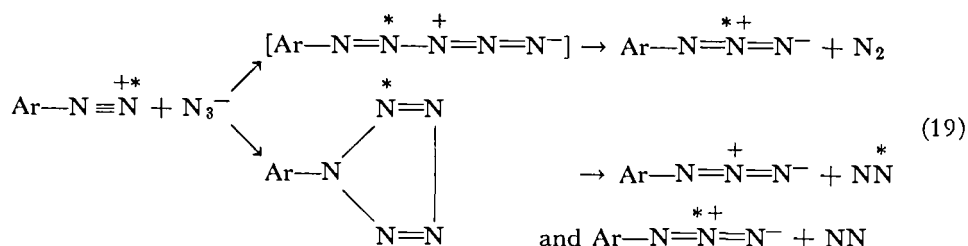


is already substituted, however, elimination to give an azide (Eq. 18) occurs so easily that the initial coupling products can seldom be isolated.⁷⁷ Most of the known examples of coupling to give a hexazadiene involve reaction of a secondary hydrazide, $\text{RCO}-\text{NHNH}-\text{COR}$.⁷⁶

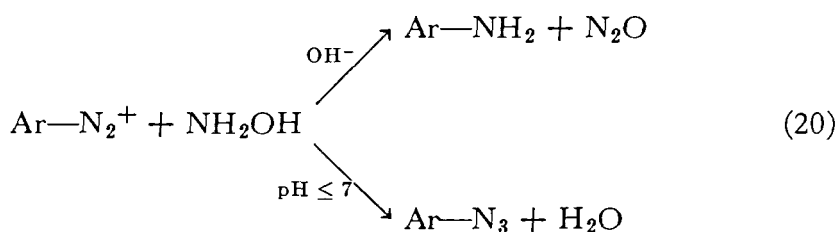


The coupling of diazonium salts to hydrogen azide (or azide ion) occurs very rapidly, and is usually complete in seconds at 0°. It first gives unstable substances of the formula $\text{Ar}-\text{N}_5$, which decompose spontaneously below room temperature to an aryl azide and nitrogen (Eq. 19). Kinetic studies of the evolution of nitrogen reveal that two distinct species are present, each of which decomposes at a distinct rate by a first-order process.⁷⁸ The more stable of these intermediates has been isolated in several instances; the fact that substitution of ^{15}N at appropriate sites in the reactants reveals only three different kinds of

nitrogen in these compounds indicates that they are arylpentazoles; the less stable intermediates, which have not been isolated and in which the separate identity of each of the five kinds of nitrogen is preserved, must be diazoazides, having a straight chain of five nitrogens.



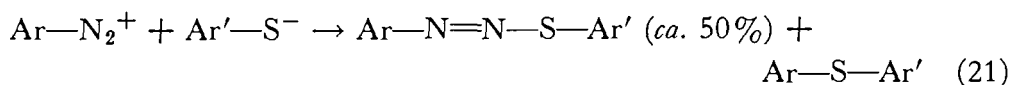
Hydroxylamine couples with diazonium salts presumably to give hydroxytriazenes, but they have not been isolated. Elimination of water to leave an aryl azide occurs rapidly. When the coupling is accomplished in basic solution, however, the principal products are the aryl amine and nitrous oxide (Eq. 20), notwithstanding the fact that coupling in acid or neutral solution followed rapidly by addition of base gives only azide.⁷⁹ Presumably prototropy is involved, for the formation of nitrous oxide



and amine corresponds to the decomposition of the nitrosohydrazine tautomer.

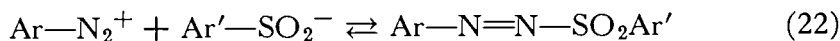
For coupling with other nitrogen compounds, the chapters dealing with them should be consulted. The chemistry of the coupling products (triazenes, pentazadienes, etc.) is discussed in Chapter 12.

COUPLING TO SULFUR AND OXYGEN Coupling to sulfur occurs with thiophenols in moderate yield (Eq. 21), but a serious competing reaction is displacement of the diazonium moiety to produce a diaryl sulfide.⁸⁰

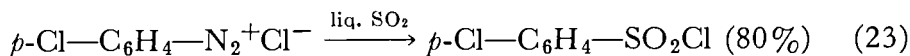


With alkyl mercaptans, such displacement is almost the sole reaction. Reduced sulfur need not be anionic, only nucleophilic, in order to displace the diazonium moiety, as shown by reaction with tetramethylthiourea, which gives S-arylisothiuronium salts.^{81, 82} Sulfur in the +4 oxidation state, as sulfite or sulfinate, couples readily to give diazosul-

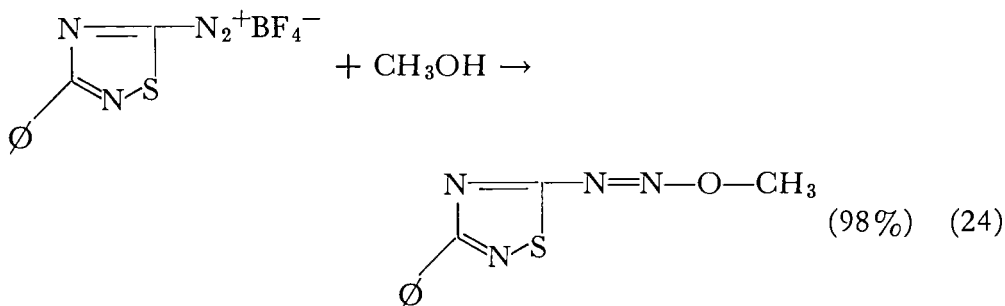
phones⁸³ (Eq. 22) or diazosulfonates⁴³; displacement does not appear to be important, except in liquid sulfur dioxide, where sulfonyl chlorides are



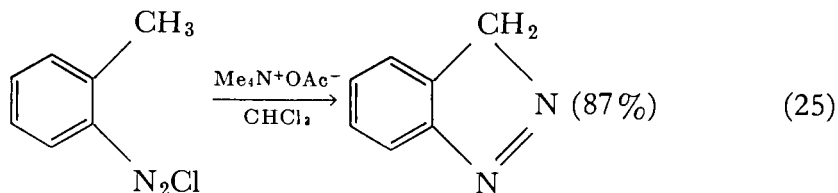
formed in good yield⁸⁴ (Eq. 23).



Coupling to the oxygen of hydroxyl groups has been reported in very few instances, apart from the diazotate equilibria discussed earlier. Formation of diazoacetates from diazonium and acetate ions has been estimated to have a very unfavorable equilibrium constant (*ca.* 10^{-5}).^{85a} Formation of diazoethers by coupling with alcohols (Eq. 24) is quite exceptional⁸²; coupling to a naphthol oxygen has been claimed.^{85b} The formation of diazoanhydrides by coupling of diazonium salts with *anti*-diazotates is another example.^{7b}

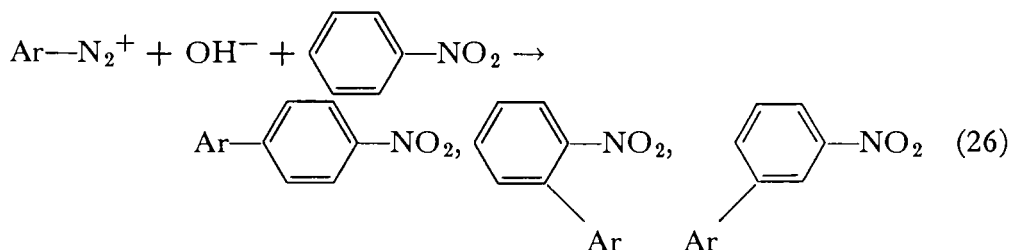


Coupling to nitrogen or to sulfur, and to some extent to carbon, can take place internally to an *ortho* substituent, forming benzotriazoles, benzothiadiazoles, or indazoles, respectively, or analogous six-membered rings.⁸⁶ Whereas coupling to sulfur or nitrogen presumably involves the diazonium ion as usual, coupling to an *ortho* methyl group (Eq. 25) is a different process, involving the diazohydroxide or diazoacetate rather than the cation.



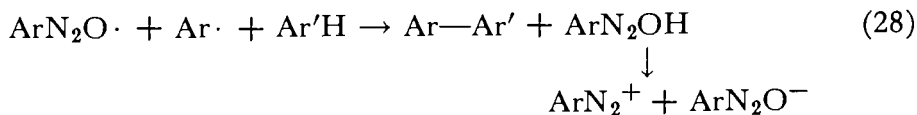
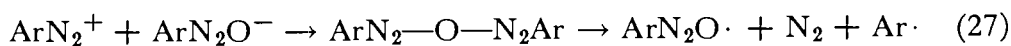
C-ARYLATION REACTIONS Diazonium salts might be expected to give rise to radicals, free or caged, either by reduction, which will be taken up in its own right further on, or by coupling to form a diazo compound that loses nitrogen easily. Aryl radicals so produced might reasonably be expected to attack trigonal carbon in benzene rings or olefins and thus

function as arylating agents. The principal species that are actually believed to behave as sources of aryl radicals are the diazoanhydrides, diazoamines (triazenes), and diazoacetates, all of which can arylate aromatic compounds to form biaryls. The evidence for the radical nature of the reactions is that such compounds (or, more often, reaction mixtures in which they may be expected to be present in equilibrium) readily arylate such substances as nitrobenzene largely in the *ortho* and *para* positions (Eq. 26), somewhat less than 10% in the *meta* position, and in about the



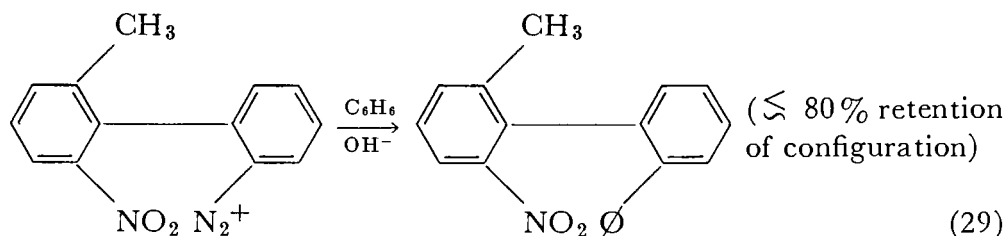
same ratio as other sources of aryl radicals, such as dibenzoyl peroxides.⁸⁶ Furthermore, nitrobenzene is three times as reactive as benzene toward arylation.^{87c} Since nitrobenzene is attacked by electrophilic reagents almost exclusively in the *meta* position, and then only with difficulty, attack by aryl cations cannot account for the observed results. Furthermore, toluene is also arylated relatively indiscriminately. On the other hand, analysis of the partial rate factors for attack at the *meta* position on a series of aromatic substrates reveals that the presumed aryl radicals have some electrophilic character when they bear a nitro group, although not when they bear only a methyl or methoxy group.^{87d}

This type of reaction, known as the Gomberg-Bachmann biaryl synthesis, is of appreciable synthetic value⁸⁸; it can be used to arylate heterocyclic as well as benzene nuclei. There appears to be an optimum pH (minimum stability) for each diazonium ion, corresponding roughly to that estimated to give rise to equal amounts of diazonium and diazotate ions, when the reaction is conducted with diazonium salt and alkali. A free-radical chain reaction starting with the corresponding diazoanhydride has been proposed to account for the second-order kinetics of nitrogen evolution⁸⁹ (Eqs. 27, 28). The use of diazoacetates, obtained either



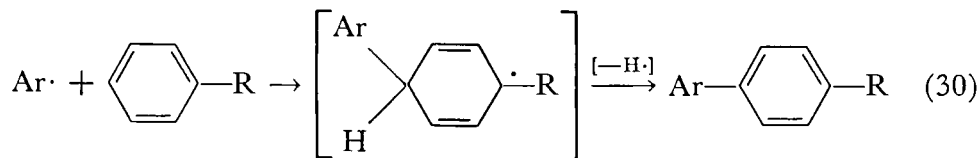
by adding sodium acetate to diazonium salt solutions or by allowing N-nitroso acetanilides to isomerize (see Chapter 15), appears to have advantages.⁸⁸

Notwithstanding the evidence for homolytic reaction just discussed, the mechanism of arylation has been controversial. This is so because some of the consequences that might be expected from the formation of free radicals are not observed, most important among them being formation of biaryls derived entirely from the diazonium compound by dimerization of the postulated aryl radicals, and the decomposition of acetoxy radicals into carbon dioxide and methyl radicals. The concept of caged ("crypto") radicals has often been invoked, but evidence has accumulated against it. The chain-reaction explanation (Eq. 28) involving diazoanhydrides can also be adapted to the case of diazo acetates (and thus nitrosoanilides); the formation of acetoxy radicals is thus not required, and the difficulty over the lack of their decomposition disappears. The aryl radicals are evidently too reactive to reach a concentration allowing significant dimerization. A pertinent fact is the behavior of optically active 2-methyl-6-nitrobiphenyl-2'-diazonium salts,⁹⁰ in which the presence of the diazonium moiety or a group of similar bulk is necessary to prevent loss of activity by rotation of the phenyl groups (Eq. 29). Formation of a free radical with a lifetime



sufficient for several molecular collisions should result in extensive racemization, but very little was observed in the presumably homolytic reaction studied. Aryl radicals have been intercepted with iodine, however.^{91b}

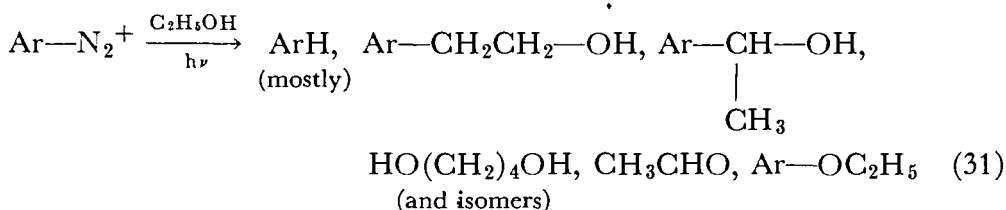
The mechanism of homolytic arylation presumably involves addition of $\text{Ar}\cdot$ to $\text{Ar}'\text{—H}$, forming a cyclohexadienyl radical, from which a companion radical ($\text{HO}\cdot$, $\text{AcO}\cdot$, or $\text{Me}_2\text{N}\cdot$) or catalyst-oxidizing agent (e.g., CuCl_4^-) removes a hydrogen atom, leaving a biaryl⁹¹ (Eq. 30). Arylation by diazonium salts can indeed be accomplished in acid solution



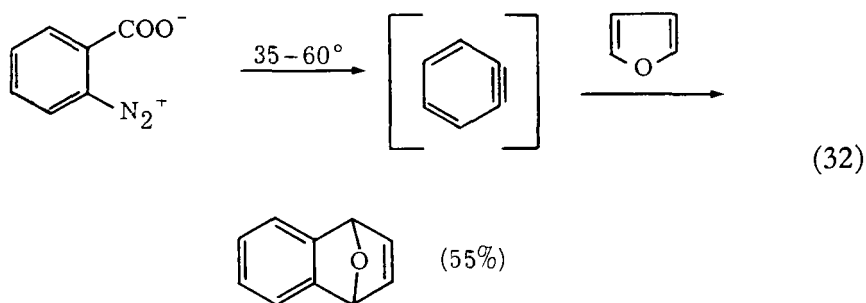
with a copper-salt catalyst (so-called "Meerwein conditions").^{92, 93} That this is a closely related case of homolytic arylation, in which $\text{Ar}\cdot$ is probably generated from reduction of Ar—N_2^+ by Cu^{I} , is demonstrated by the fact that the partial rate factors that determine the orientation of

the substitution are the same for Meerwein arylation as for arylation with nitrosoacetanilide.⁹³ A further method of arylation, warming dry diazonium chlorides with an aromatic hydrocarbon and aluminum chloride—seems likely to be a heterolytic process, but it has not been studied sufficiently for a conclusion to be drawn. Formation of aryl chloride is a competing and sometimes completely dominant reaction.⁹⁴

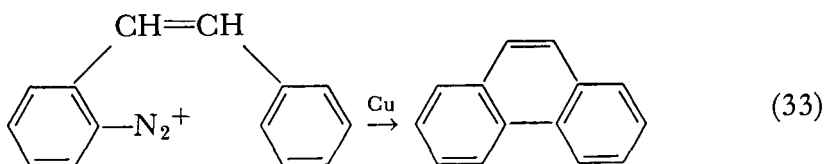
Whether or not the foregoing arylations involve free or caged radicals, it seems very probable that free radicals can be formed from diazonium salts by other processes, particularly photolysis.⁹⁵ Irradiation of diazonium salts in ethanol (Eq. 31), for example, gives rise to products



difficult to account for otherwise.⁹⁵ Mention should also be made of the formation of benzyne as the reactive intermediate in the thermal and photolytic decomposition of dry diazotized anthranilic acid.^{95b}

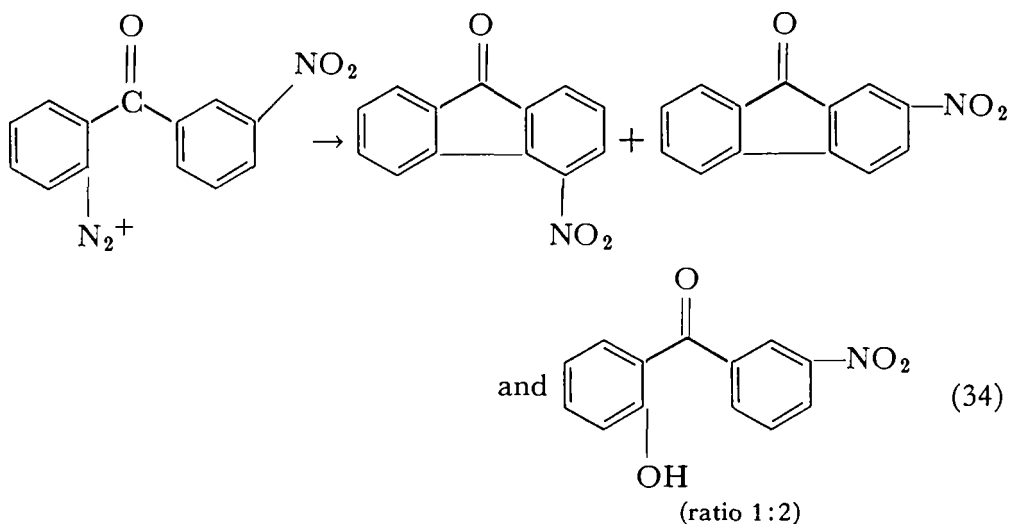


PSCHORR CYCLIZATION Intramolecular arylation is an important synthetic route to fused-ring compounds, both carbocyclic and heterocyclic. In its simplest and oldest form, diazotized *o*-aminostilbenes cyclize to phenanthrenes under the influence of a copper catalyst (Eq. 33), in what is known as the Pschorr reaction.⁹⁶ The requirement of a copper catalyst, whose mode of action is discussed further on, strongly suggests that



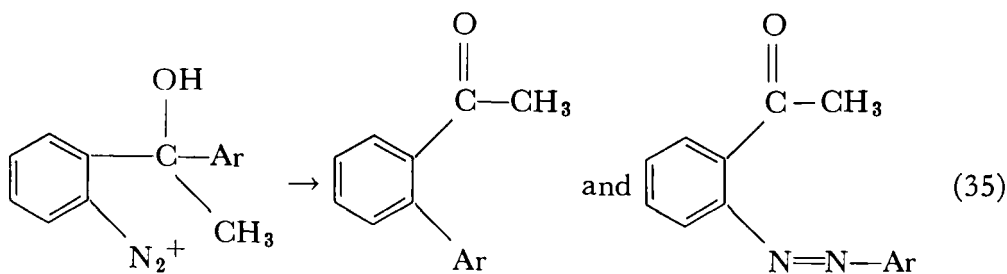
this is a homolytic process. On the other hand, there are many examples of analogous ring closures that proceed in acid solution without a catalyst, and it seems very likely that such reactions are heterolytic, proceeding

through an aryl cation. The formation of 9,10-benzophenanthrene from diazotized 2-amino-2'-phenylbiphenyl, for example, occurs in strong sulfuric acid solution without a copper catalyst in better yield than under Gomberg-Bachmann conditions (pH 11-13).⁹¹ Furthermore, the cyclization of diazotized *o*-aminobenzophenones to fluorenones (Eq. 34) is markedly depressed by the presence of a 3'-nitro group in



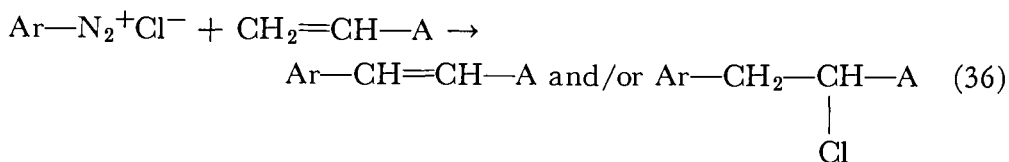
favor of solvolysis to a phenol⁹⁷; homolytic cyclization should have been promoted by such substitution. It would appear that both homolytic and heterolytic cyclization is possible, but for any specific case, one path may be markedly easier than the other.

A rearrangement reaction related to these heterolytic cyclizations occurs with diazotized *o*-aminobenzhydrol derivatives. An aryl group migrates from the carbinol carbon to the site of the diazonium moiety, in a process reminiscent of the pinacol rearrangement, producing a carbonyl compound,⁹⁸ along with an analogous product of coupling with electrophilic displacement (Eq. 35).



MEERWEIN ARYLATION Arylation of unsaturated compounds by diazonium salts with the aid of copper catalysts is known as the Meerwein arylation reaction.⁹⁴ The product is either the aryl olefin, or the saturated compound resulting from the addition of Ar and Cl to the double bond,

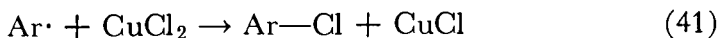
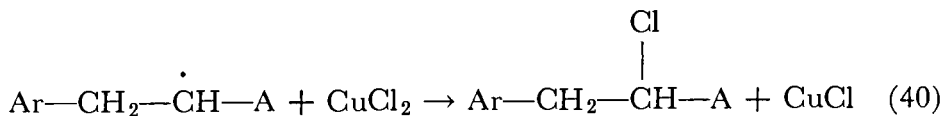
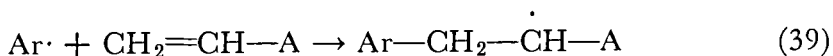
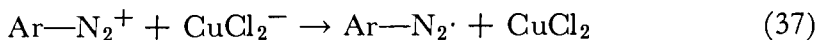
or both (Eq. 36). The reaction proceeds best when there is an activating group, usually carbonyl, cyano, or aryl, attached to one of the olefinic carbons, but even then, yields are modest at best. As noted in Chapters 8 and 9, aldoximes and aldehyde semicarbazones can also be arylated



(replacement of aldehyde hydrogen) by diazonium salts.

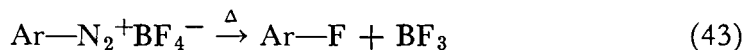
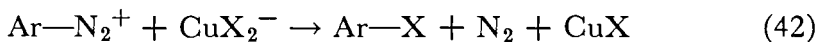
The mechanism of the Meerwein arylation has been extensively studied, but it remains enigmatic. The collected evidence strongly implies a homolytic process, perhaps *crypto* radical in nature, but interpretation is beclouded by apparent inconsistencies and contradictions in the reported facts. The orientation of attack, in which the aryl group enters β to the activating group, and the markedly greater reactivity of olefins bearing electron-withdrawing groups, are consistent with free-radical and not electrophilic attack. Kinetic measurements of the rate of nitrogen evolution have revealed that the reaction is retarded by air; in the presence of air, unsaturated compounds retard the evolution of nitrogen from 2,4-dichlorobenzenediazonium chloride, but in the absence of air, the apparently first-order reaction is mildly accelerated (*ca.* doubled in rate) by acrylates and acrylonitrile.⁹⁹

Although a homolytic reaction is indicated, it is not immediately obvious why other consequences of the formation of free radicals, particularly radical-induced polymerization of olefins, are not observed, nor why the rate of the reaction should be sensitive to the olefin. Furthermore, the function of the copper compounds as catalysts is confusing, for in some cases cuprous chloride complexes appear to be required, in others, cupric. Most of these objections are handled in a mechanism^{92, 99, 100} in which aryl radicals are generated by reduction of the diazonium ion by Cu^{I} , perhaps in the form of copper-olefin-chloride complex (Eq. 37). The absence of induced polymerization is attributed to interception of the



aralkyl radicals by Cu^{11} (Eq. 40) before they can propagate a radical chain. The scheme as outlined in Equations 37–41 is at best only a rough approximation, in which no attempt is made to indicate the form of the presumed olefin-Cu complex; furthermore, part or all of the process may take place in one reaction sphere (i.e., as caged radicals). The Sandmeyer reaction, leading to chlorobenzenes, is of course always a competing process, as indicated. The formation of aryl olefin in the product can be envisaged as arising either from dehydrohalogenation of the saturated adduct, or from oxidative removal of a hydrogen atom from the species $\text{Ar}-\text{CH}_2-\dot{\text{C}}\text{H}-\text{A}$.

SANDMEYER REACTION The problem of catalysis in the Meerwein reaction is inseparable from that of similar catalysis in the Sandmeyer reaction. In this well-known reaction, aqueous solutions of diazonium salts are induced to yield aryl chlorides, bromides, or cyanides by treatment with the appropriate cuprous salt (Eq. 42). Replacement of the diazonium moiety by some groups, notably iodide, proceeds without a catalyst, and in other cases, indeed, catalysis appears to be essentially ineffective. Replacement by fluoride is such a case; this process is best accomplished by allowing dry diazonium fluoborates or fluorophosphates to decompose under the influence of gentle heat (Eq. 43) and is known as the Schiemann reaction.¹⁰¹



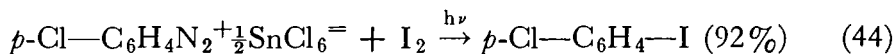
The mechanism of the Sandmeyer reaction cannot yet be regarded as certain. There is much to suggest a similarity to the Meerwein arylation, and indeed, a very plausible mechanism can be constructed on that basis,¹⁰⁰ in which the role of the catalyst is the same, namely, to set in motion a free-radical chain by reducing some diazonium salt to aryl radicals. There is, however, the same difficulty about the appearance of true free radicals as in the Meerwein reaction. The Sandmeyer reaction on optically active biphenyls, for example, gives a product that retains 80–90% of the optical activity, in cases where the presence of the diazonium moiety or halogen is necessary to prevent racemization.⁹⁰

Nevertheless, the role of the catalyst in Sandmeyer reactions¹⁰² has been a subject of controversy for decades, and it has even been questioned whether the actual catalyst is Cu^0 , Cu^1 , or Cu^{11} . From the accumulated evidence, it appears very probable that a cuprous species, CuX or CuX_2^- , is the actual catalyst, and that the occasionally successful use of copper powder or cupric salts is a result of oxidation by air or reduction by organic components, generating the required cuprous catalyst. Kinetic investigations^{103, 104} of the formation of aryl chlorides have shown that

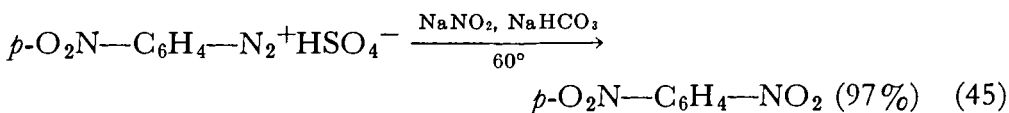
the rate is *inversely* proportional to the chloride concentration. This almost certainly indicates the removal of the active catalytic agent by a reaction that consumes two chloride ions. If CuCl_2^- is the active agent, it might be converted to $\text{CuCl}_4^=$, and if CuCl is the catalyst, conversion to $\text{CuCl}_3^=$ would be implied; the question appears not yet to have been resolved.

Sandmeyer reactions are subject to various side reactions, and the crude products are often colored. The principal by-products are the biaryl and azo compounds; these are, of course, reduction products (*vide infra*). The rate of their formation depends on the square of the cuprous catalyst concentration. From this fact and the rate dependence of the main reaction on $[\text{Cl}^-]$, optimum conditions¹⁰⁵ demand a low catalyst concentration and the avoidance of a large excess of the anion.

The replacement of the diazonium moiety by iodine, which proceeds spontaneously at room temperature without a catalyst, can be interpreted as a result of the low oxidation potential of iodide ion, which could allow it to reduce diazonium ions to radicals, or the high nucleophilic activity of iodide, which would lead to enhanced ability to displace N_2 compared to chloride. Since cyanide, which is also a good nucleophile but is not as good a reducing agent, does not convert diazonium salts to nitriles without a catalyst, the former interpretation seems more likely. Better yields of aryl iodide have been reported^{95a} from the photolysis of diazonium chlorostannates in solutions of I_2 (Eq. 44), but the process is not nearly so simple to carry out.

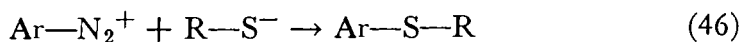


In contrast to the replacement of the diazonium moiety by halogen or cyano, which is reliable and widely applicable, replacement by nitro by reaction with nitrites is of erratic applicability. The process has been studied extensively for the purpose of developing a general preparative procedure, and in favorable cases, high yields can be obtained (Eq. 45). The best method to date consists of adding a diazonium solution rapidly

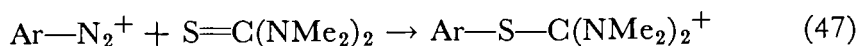


to a warm solution of sodium nitrite buffered with sodium bicarbonate,¹⁰⁶ with or without a cuprous oxide catalyst.

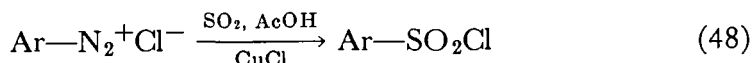
Replacement by reduced sulfur⁸⁰ can be accomplished advantageously by allowing diazonium salts to react with mercaptides (Eq. 46), although thiophenols give mostly coupling products, as was mentioned earlier.



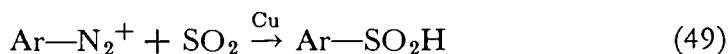
Displacement by the sulfur of tetramethylthiourea^{81, 82} yields a product hydrolyzable to a thiophenol (Eq. 47). The solvolysis of diazonium chlorides to sulfonyl chlorides in liquid dioxide was also mentioned earlier.



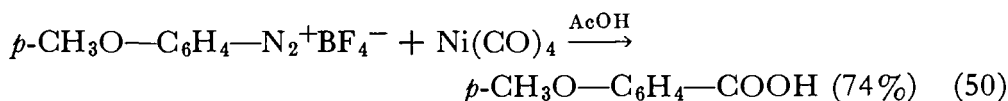
The same transformation can be accomplished more simply by adding an



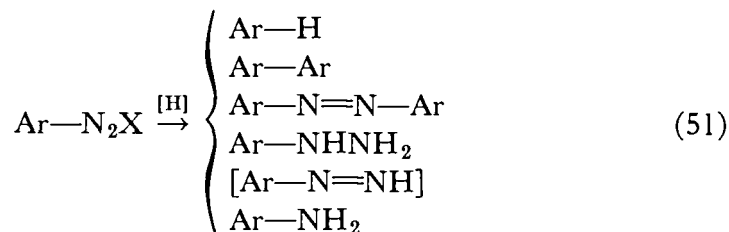
aqueous diazonium chloride solution to one of sulfur dioxide in glacial acetic acid in the presence of a cuprous chloride catalyst¹⁰⁷ (Eq. 48). With a powdered copper catalyst, reductive displacement takes place instead, yielding sulfinic acids¹⁰⁸ (Eq. 49).



By means of nickel carbonyl in glacial acetic acid, diazonium salts can be converted into carboxylic acids¹⁰⁹ (Eq. 50).



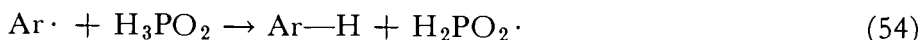
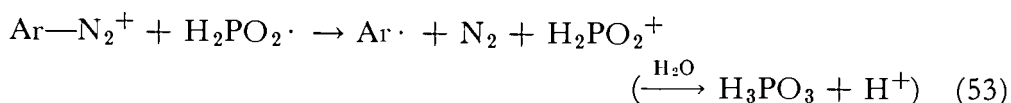
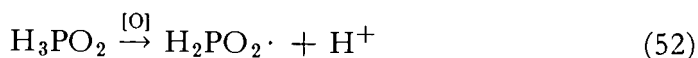
REDUCTION Reduction of diazonium salts can be managed so as to accomplish replacement by hydrogen, biaryl or azobenzene formation, or addition of hydrogen to form hydrazines, diimides, or the parent amine (Eq. 51). Only the first of these is fairly general. Furthermore,



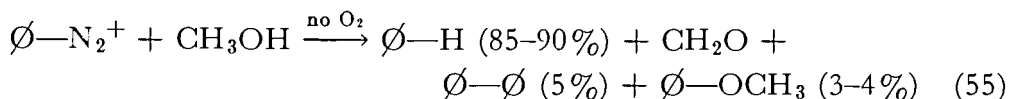
reduction may be involved as part of a different process, such as the Meerwein arylation, or may be an intramolecular process.

Replacement of the diazonium moiety by hydrogen, often called deamination when combined with the diazotization step, is a widely used reaction in synthesis and structure proof.¹¹⁰ It is usually accomplished with hypophosphorous acid; traces of oxidizing agents have a catalytic effect.¹¹¹ There is much evidence to suggest that this reaction is a free-radical chain process (Eqs. 52-54). The kinetic isotope effect in D_2O

(k_H/k_D between 2 and 6) is in accord with such a path.¹¹² Reduction by

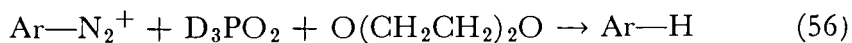


alcohols has also been used, but it is erratic, often unclear, and its history is beset with contradictory reports. The explanation is that this, too, is a free-radical chain reaction and as such is strongly inhibited by atmospheric oxygen.¹¹³ In the complete absence of air and in buffered solution, reduction by methanol can occur in high yields (Eq. 55), whereas in acid solution open to the air, solvolysis takes place almost exclusively. Since deuterium is not incorporated in the reduction product when $\text{C}_2\text{H}_5\text{OD}$



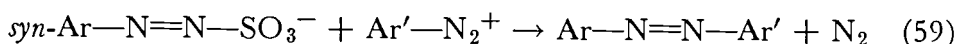
is used, it can be concluded that the hydrogen for reduction comes from the α -carbon. Reduction by hydroquinone,¹¹⁰ which is presumably also a free-radical chain reaction, probably involves removal of hydrogen from oxygen, however.

Ethers, such as dioxane, dioxolane, diglyme, and tetrahydrofuran, have been found to be good hydrogen-donating agents toward decomposing diazonium salts, and reductions to hydrocarbon in yields as high as 80% have been achieved.¹¹⁴ This type of reaction has been interpreted¹¹⁴ as an ionic process, in which an aryl cation picks up hydride from the ether, leaving a carbonium ion that is stabilized by the adjacent oxygens. Under other conditions in which a diazonium salt is treated with hypophosphorous acid in the presence of dioxane, a free-radical process is believed to obtain.¹¹⁵ It has been shown by the use of D_3PO_2 under the latter conditions that the hydrogen in the product comes from the dioxane, presumably through attack by $\text{Ar}\cdot$, and not from D_3PO_2 (Eq. 56).



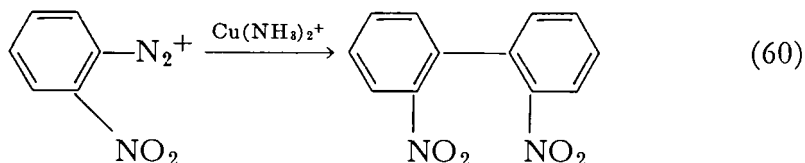
Reduction by dialkylamides is a comparatively recent and quite successful development. Tetramethylurea¹¹⁶ and dimethylformamide¹¹⁷ are the usual reagents. It has been reported that the former reagent gives good results with diazonium salts bearing electron-withdrawing substituents, but that hypophosphorous acid or alkaline formaldehyde give better results when electron-donating substituents are present. The

by the interaction of diazonium salt with a *syn*-diazosulfonate ¹²¹ (Eq. 59);

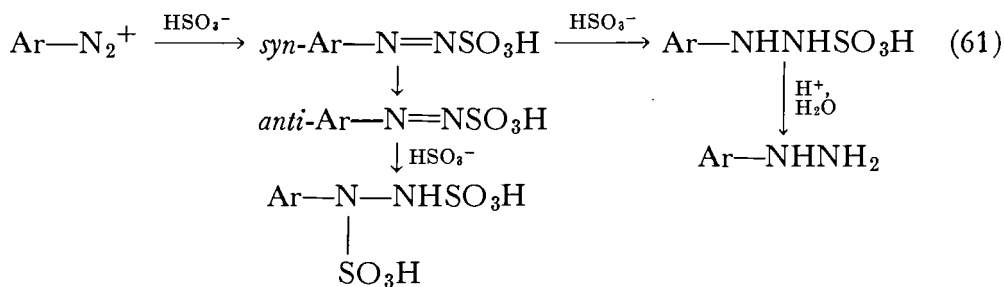


the evolved nitrogen, interestingly, was found to come from the diazonium ion.

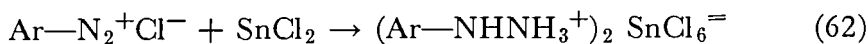
Reduction to biaryls (Eq. 60) is occasionally of considerable synthetic value, as in the preparation of diphenic acid, but its generality is sharply limited by the competing formation of azobenzenes,¹²⁰ whose occurrence appears to depend principally on structure and to be little influenced by experimental conditions insofar as these have been explored.



Reduction to hydrazines has been mentioned in Chapter 9 as an important preparative method for aryl hydrazines. The two general methods, formation and further reduction of diazosulfonates,¹²² and direct reduction with stannous chloride,¹²³ are both fairly general and usually give good yields, although the paths are considerably different. *syn*-Diazosulfonates are reduced by excess bisulfite to arylhydrazine sulfonic acids, which can be hydrolyzed easily in acid solution (Eq. 61); the *anti*-diazosulfonates are also reduced, but arylhydrazine disulfonic acids are formed.^{124, 125} Stannous chloride reduction perhaps passes through the aryldiimide stage, Ar-N=NH ; the final products often crystallize as



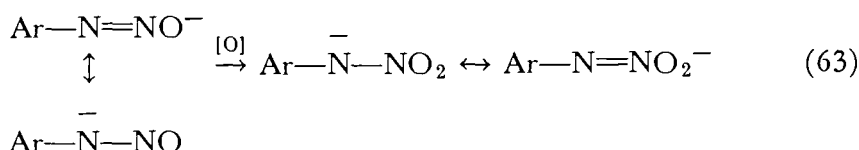
chlorostannite or chlorostannate salts (Eq. 62).



Reduction of diazonium salts to amines, a reaction of little or no practical importance, has been accomplished with sodium amalgam and acetic acid ¹²⁶ and in one case, benzene-1,2-*bis*-diazonium chloride, with stannous chloride.¹²⁷

OXIDATION Diazonium salts have been oxidized in alkaline solution as diazotates, as have aliphatic diazotates (prepared from nitroso hydra-

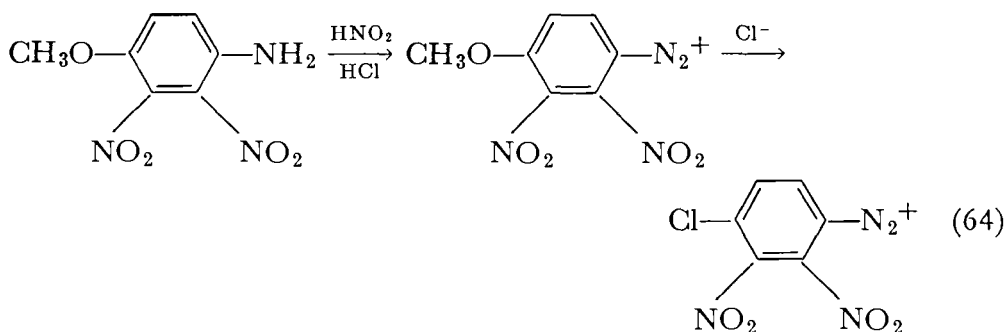
zines—see Chapter 15). The products are arylnitramides (actually, their salts) ¹²⁸ (Eq. 63); their formation is best looked upon as the addition of a second oxygen to a nitrosamine (whose anion is indistinguishable from the diazotate ion). The preferred oxidizing agent is ferricyanide, al-



though permanganate, tribromide, and hydrogen peroxide have been used. The last oxidizing agent can also be made to undergo coupling to give diazoperoxides.¹²⁹

Alkylation of diazotate salts,^{130, 131} which can give either diazo ethers (from Ag salts) or nitrosamines (from Na salts), is discussed in connection with N-nitroso compounds (Chapter 15).

SUBSTITUENT EFFECT The powerful electron-withdrawing ability of the diazonium ion was mentioned under "Properties." An important practical result of this effect is that nucleophilic displacement of potentially anionic groups *ortho* or *para* to a diazonium function occurs particularly easily.¹³² When the effect of the diazonium function is augmented by a nitro group *ortho* to the displaceable group, displacement can occur in cold aqueous solution (Eq. 64), even during the diazotization step itself.¹³³ The effect of the diazonium group is greater than either a nitro or a quaternary ammonium substituent¹³⁴ and approaches that of two



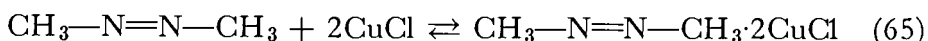
nitro groups. Displaceable groups include alkoxy, nitro (as nitrite ion), sulfo (as bisulfite ion), and halogen, whose activity is in the expected order $\text{I} > \text{Br} > \text{Cl} > \text{F}$ ^{37a}; N_2 is also displaceable, and tetrazotized *p*-phenyldiamine undergoes loss of one diazonium function by displacement particularly easily.

B. Azo Compounds ¹³⁵

The chemistry of aromatic azo compounds (azobenzene derivatives) is limited largely to oxidation, reduction, and cycloaddition reactions.

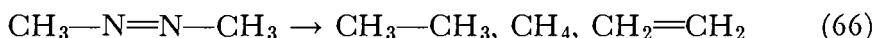
Aliphatic members, on the other hand, have a richer chemistry that includes tautomerism to hydrazones, loss of nitrogen, and in suitable cases, functioning as electrophilic agents.

The ability of azo compounds to form salts is so weakly developed that few salts have been isolated.¹³⁶ Complex compounds with transition metal salts, particularly cuprous chloride (Eq. 65), are well known, however; since they are usually easily broken up by heat, they serve as useful solid derivatives for the isolation of azo compounds, particularly the

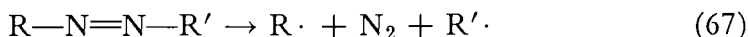


volatile aliphatic members.¹³⁷ The ratio of azo compound to metal salt is always integral, but is often other than 1:1.¹³⁸

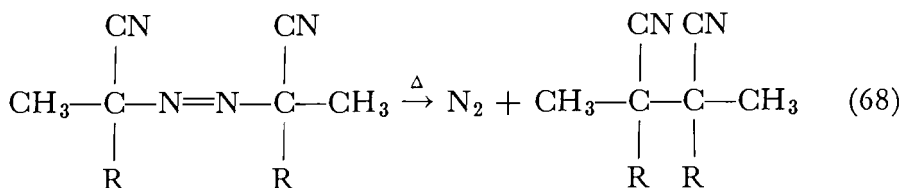
THERMOLYSIS Azo compounds are decomposed by heat or by near-ultraviolet radiation with an ease that varies with the expected stability as free radicals of the groups attached to nitrogen; azobenzenes are the least readily decomposed. The products can be accounted for quite satisfactorily on the basis of a simple cleavage into molecular nitrogen and two radicals if the additional assumption is made that the two radicals have a greatly enhanced probability of combining with each other as a consequence of having been generated in the same solvent "cage." Dimers are, indeed, generally the major products,¹³⁹ usually accompanied by disproportionation products and compounds formed by abstracting hydrogen from the environment^{139b} (Eq. 66). Thermal decomposition



is first order,^{139, 140} and has an unusually high activation energy (40–50 kcal/mole). There is a large secondary isotope effect upon α -deuteration of certain symmetrical azo compounds, in which, it has therefore been concluded, both C—N bonds may break simultaneously¹⁴¹ (Eq. 67). Further evidence is found in the observation that substituted azoiso-



butyronitrile derivatives decompose at the same rate whether the *meso* form or the racemate is used, and the substituted succinonitriles produced (Eq. 68) have the same stereoisomeric composition regardless of the con-

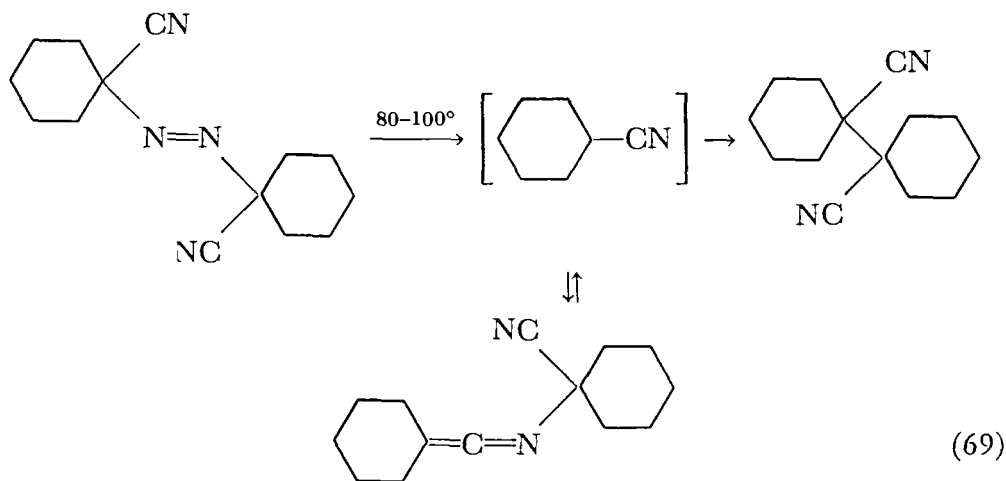


figuration of the starting material.¹⁴² The fact that decomposing azo compounds induce polymerization of olefins is not only evidence for the

free-radical nature of the decomposition,¹⁴³ but, indeed, has become the basis for widespread industrial use of azoisobutyronitrile ("AIBN") and related compounds as initiators.

The high efficiency of recombination of radicals when azo compounds are decomposed in solution and its implication of a cage effect has stimulated intensive investigation. Since radicals that recombine inside the same solvent cage in which they were formed are not active in other ways, such as polymerization initiation or combination with radical scavengers, it is possible to investigate experimentally the relative efficiency of free-radical production and the cage effect. An interesting example is a study of α -azo amidines, which can be studied as the free bases, the mono-cations, or the di-cations.¹⁴⁴ Protonation increases the rate of decomposition, but the increase in efficiency of free radical product is small, and not enough to establish firmly whether repulsion of like charges can seriously reduce the cage effect.

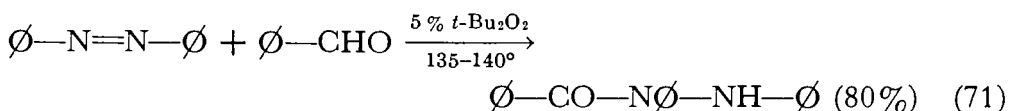
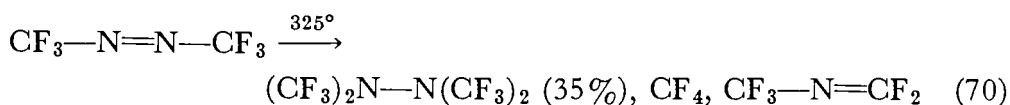
With α -azo nitriles, the possibility is presented for recombination of radicals to occur in two ways, producing either succinonitriles or ketenimines (Eq. 69). The latter products have actually been observed in



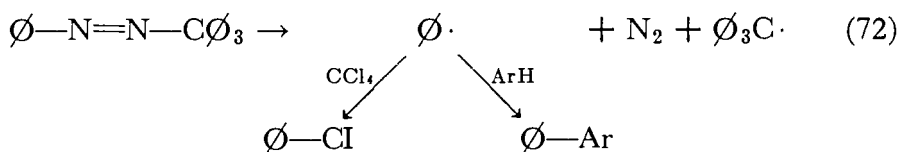
several instances. Since their rate of formation is decreased by radical scavengers, whereas their rate of disappearance (to succinonitrile) is increased by scavengers,¹⁴⁵ it has been concluded that ketenimines are formed by combination of free radicals outside the solvent cage. The reversal of this process gives back the radicals, which may recombine in either orientation, thus eventually converting all the ketenimine to the more stable succinonitrile structure.

Perfluoroazo compounds are particularly amenable to study of their decomposition in the gas phase because of their volatility and the stability of many of the products. An interesting phenomenon is the combination of undecomposed azo compound with perfluoroalkyl radicals to

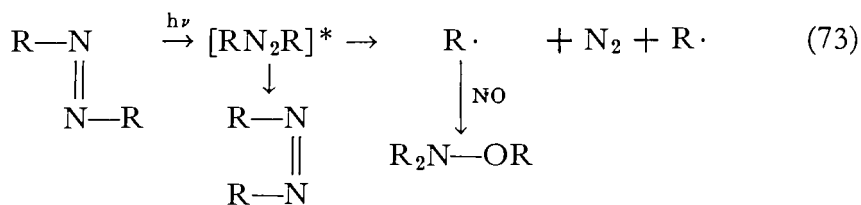
produce tetrasubstituted hydrazines in preparative yield ¹⁴⁶ (Eq. 70); such a reaction has also been observed in the free-radical addition of benzaldehyde to azobenzene ¹⁴⁷ (Eq. 71).



Aryl radicals are not readily obtainable from thermolysis of azobenzenes, but when a companion radical of unusual stability is produced concurrently, the barrier can be overcome. A suitable case is phenylazotriphenylmethane. The phenyl radicals produced in its decomposition combine with the stable triphenylmethyl radical only to a very small extent, and instead wander out of the solvent cage to attack solvent molecules ^{148a} (Eq. 72). In an aromatic hydrocarbon solvent, biaryls are produced; the orientation of the attack is essentially the same as that observed with other sources of phenyl radicals. ^{148b}

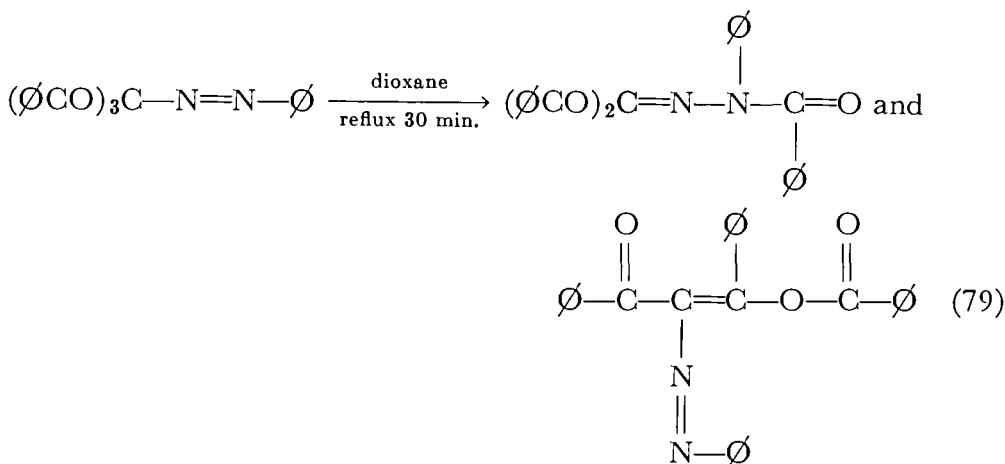


PHOTOLYSIS Photolysis of azo compounds has two distinct results: isomerization to the higher-energy *cis* configuration and cleavage into nitrogen and a pair of radicals (Eq. 73). An excited state is evidently formed first, which in the gas phase undergoes cleavage exclusively; the



quantum yield is then 1. ^{149, 150} In solution, isomerization becomes important, and it is in this way that the *cis* isomers of azobenzene, azomethane, ^{150a} etc., have been prepared. In the cleavage reaction, both C—N bonds appear to break simultaneously, and there is no evidence of intermediate $\text{R—N}_2\cdot$ radicals. ¹⁵¹ Recombination of the radicals from α -azo nitriles may occur in two ways, as with thermolysis, and as high as 35% of ketenimine has been isolated ¹⁵² (Eq. 74)

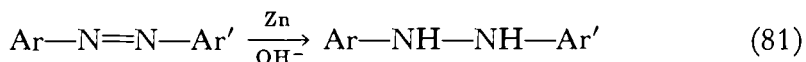
Rearrangement to a hydrazone has also been observed to occur by migration of a group other than hydrogen, in the case of phenylazotri-benzoylmethane ¹⁵⁷ (Eq. 79).



REDUCTION Reduction of azo compounds can be accomplished in a variety of ways to yield either amines or hydrazines. Catalytic hydrogenation ¹⁵⁸ (Eq. 80), sodium dithionite ^{159a} and hydrogen iodide ^{159b} give rise to amines, although hydrogenation over platinum has been stopped



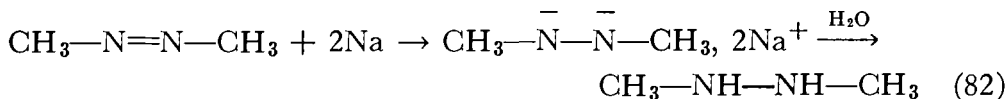
at the hydrazine stage.¹⁵⁴ Reduction to hydrazines is accomplished by sodium amalgam, sodium and alcohol,^{154, 160} aluminum amalgam,¹⁶⁰ zinc and alkali ¹⁶⁰ (Eq. 81), hydroquinone,¹⁶¹ or other hydrazines.¹⁶² Reduction by titanous chloride has been made the basis of a quantitative



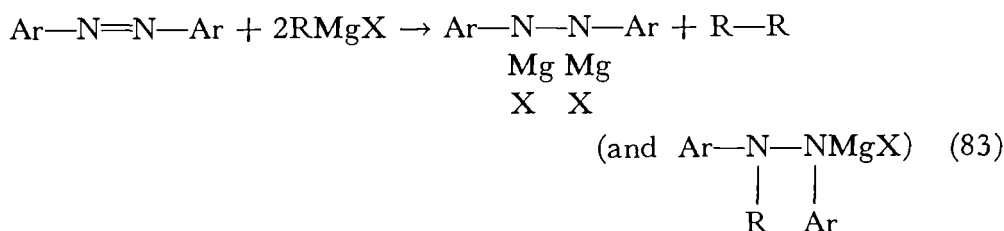
determination of azo compounds.¹⁶³ Reduction in acidic solution is usually complicated by the occurrence of the benzidine rearrangement.¹⁶⁴

There are several reduction methods that produce salts of a hydrazine dianion as the primary product, in some cases apparently through the

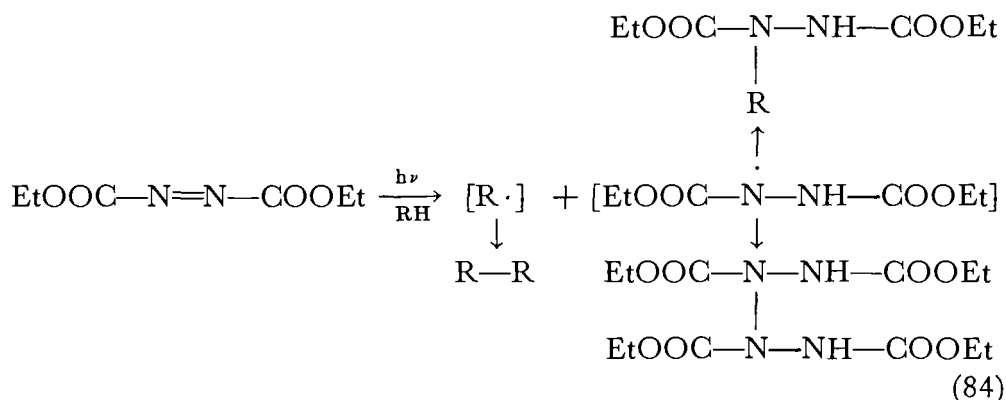
intermediate formation of an anion radical, $\text{R}-\text{N}^{\cdot-}-\text{N}^--\text{R}$. Metallic potassium ¹⁶⁵ and sodium ¹⁶⁶ are good examples (Eq. 82). Grignard re-



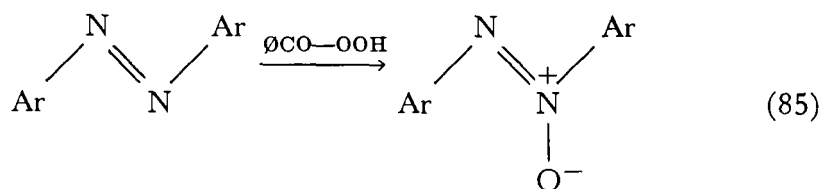
agents act largely as reducing agents toward azobenzenes, and also give salts of the hydrazine dianion ¹⁶⁷ (Eq. 83).



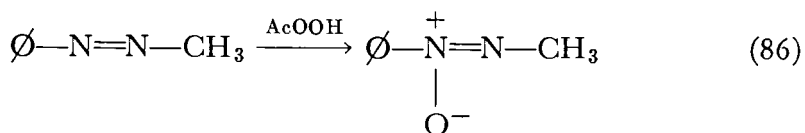
Hydrogen abstraction during photolysis is also a reductive method for azo compounds, but examples are largely confined to azodicarboxylic ester and relatives.^{161, 168} It is apparently a reaction of an excited state of the azo compound, and clearly passes through the hydrazyl radical stage ^{168b} (Eq. 84).



OXIDATION Oxidation of azo compounds in general leads to either azoxy compounds or azines. Oxidation with peroxy acids usually gives azoxy compounds in preparatively useful yields ^{169, 170} (Eq. 85); the stereochemistry of the azo compound is preserved in the products.^{9b, 52} Unsymmetrical azo compounds usually give both structurally isomeric

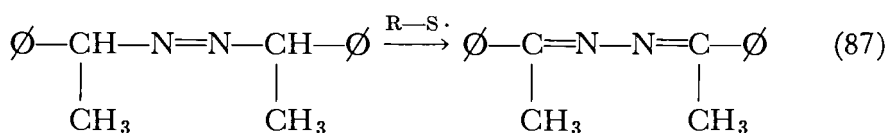


azoxy compounds, but the ratio is likely to be very one-sided, and sometimes the minor product cannot be detected.¹⁶⁹ Benzeneazomethane (Eq. 86), which may be a model for aryl alkyl azo compounds, and aryl benzyl azo compounds¹ give almost exclusively the isomer with the

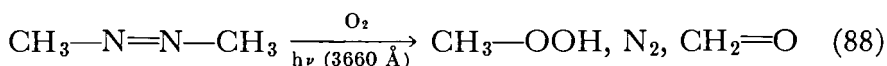


oxygen adjacent to the phenyl group.^{9b} Among azobenzenes, electron-withdrawing substituents direct oxidation to the far nitrogen.¹⁷¹ The rates of oxidation of substituted azobenzenes follow the Hammett equation with some deviation, *p*-methoxyazobenzene being faster than predicted and *p*-nitro slower.¹⁷²

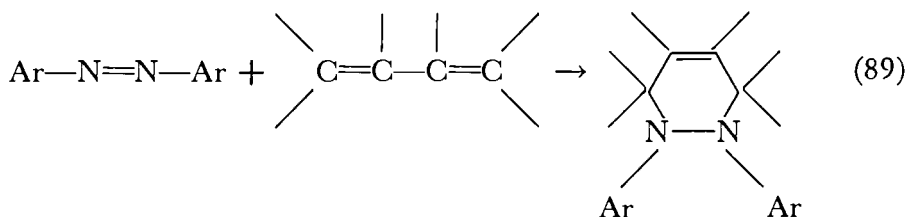
Azo compounds having α -hydrogens can be oxidized to azines by exposure to sources of hydrogen-abstracting free radicals, such as $\text{R}-\text{S}\cdot$ and $\text{Cl}_3\text{C}\cdot$ ¹⁷³ (Eq. 87). Yet another type of oxidation is observed during



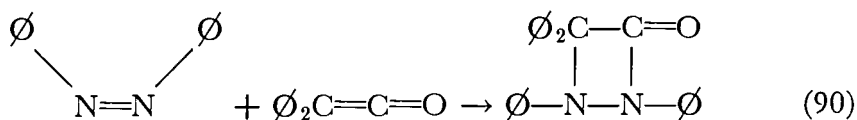
photolysis in the presence of oxygen. Methyl hydroperoxide is produced (Eq. 88), apparently from combination of methyl radicals with O_2 , followed by hydrogen abstraction, perhaps from methoxy radicals.¹⁷⁴



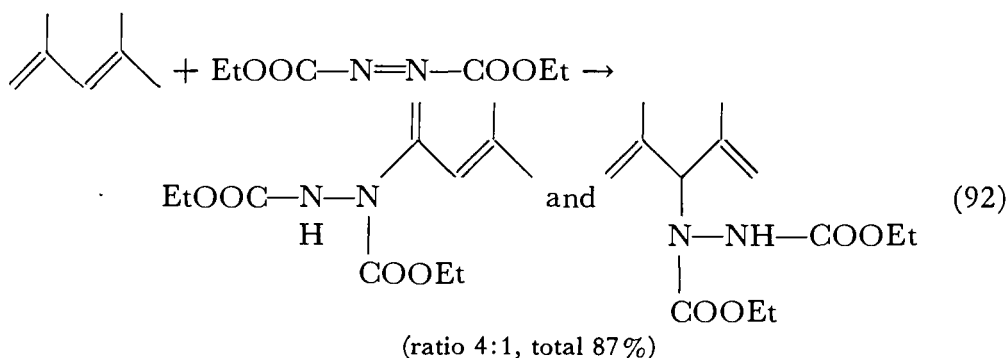
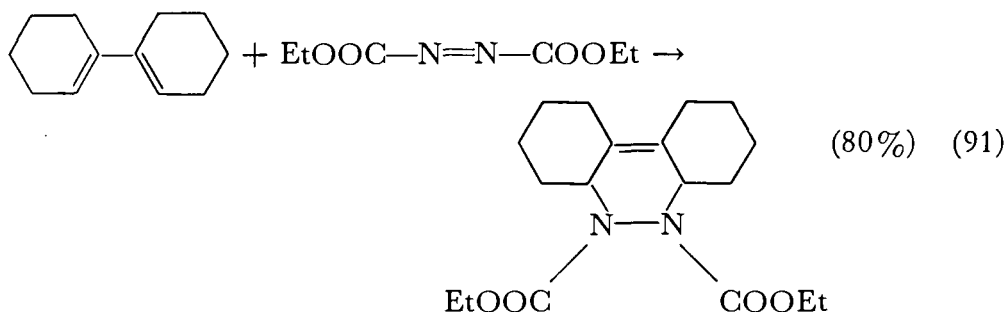
REACTIONS WITH OLEFINS Olefins react with azo compounds to give either cyclic compounds or substitution products, depending largely on the nature of the azo compound. The Diels-Alder reaction was, in fact, first observed with azo compounds, which react with conjugated dienes to produce tetrahydropyridazines (Eq. 89); the reaction goes best when the azo compound bears electron-withdrawing substitution,¹⁷⁵ and



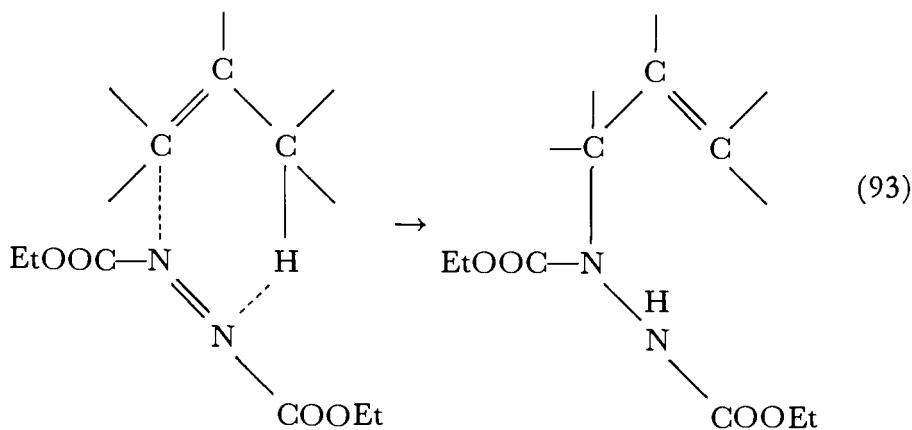
accordingly, perfluoroazo compounds react readily.¹⁴⁶ Cycloaddition to form the diazetidine ring has been observed with *cis*-azobenzene (Eq. 90), but not *trans*⁶⁶; azodicarboxylic ester reacts in a 1:2 ratio instead.¹⁷⁶



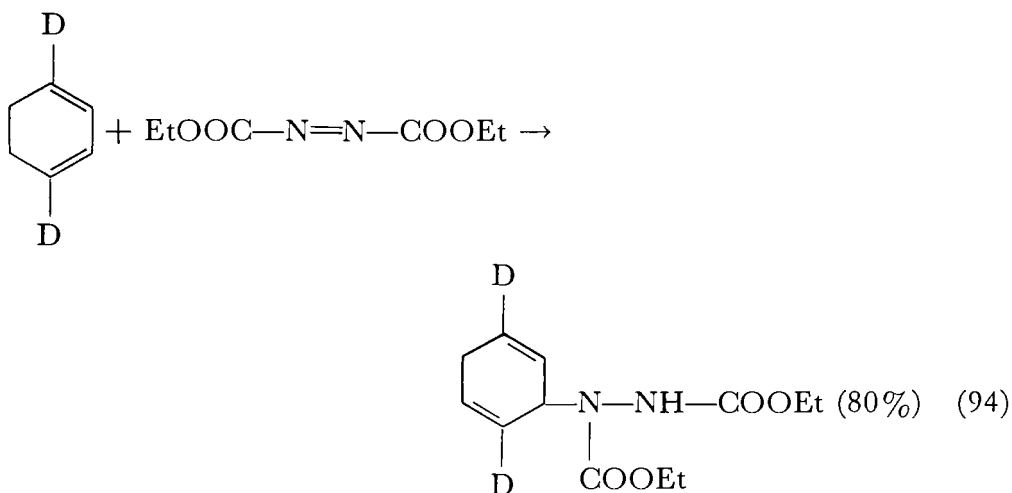
Azodicarboxylic ester, in contrast to simple azoalkanes and azobenzenes, is prone to substitute olefins at the expense of Diels-Alder addition, unless the diene is very unhindered.¹⁷⁷ Bi(cyclohexenyl), for example, gives a tetrahydropyridazine in 80% yield (Eq. 91), but 2,4-dimethylpentadiene undergoes 87% allylic substitution (Eq. 92). The substitu-



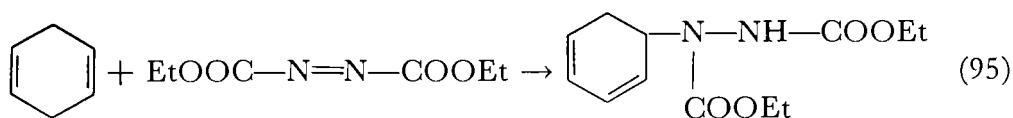
tion reaction, which is a useful source of alkyl hydrazine derivatives, also occurs readily when azodicarboxylic esters are heated with monoolefins; it always takes place at a vinyl position with concomitant shift of a double bond to give an allylic product.^{179, 180} A variety of investigations support the view that the reaction is generally a cyclic process rather than one that gives rise to free radicals or ions; that is, the hydrogen transfer is concerted with formation of the carbon-nitrogen bond (Eq. 93). How-



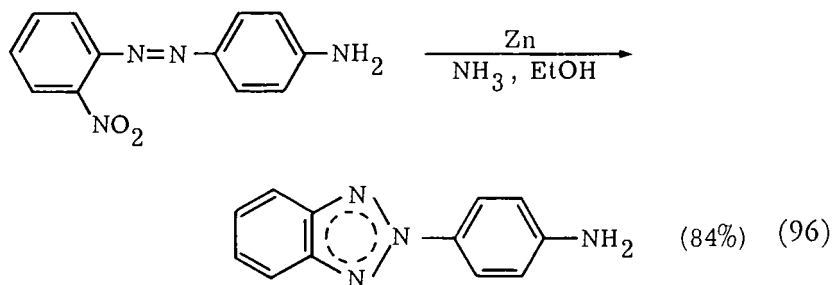
ever, an auxiliary free-radical chain reaction path, catalyzed by radical initiators, has been observed in the cases of cyclopentene and cyclohexene¹⁸⁰ and is the exclusive reaction for fluorene and tetralin. The kinetics are second order; vinyl deuterium is not disturbed (Eq. 94),



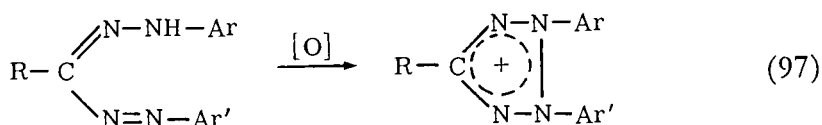
and 1,4-cyclohexadiene, which gives 80% substitution (Eq. 95), undergoes no detectable isomerization to the 1,3-isomer in unconsumed starting material.¹⁸¹



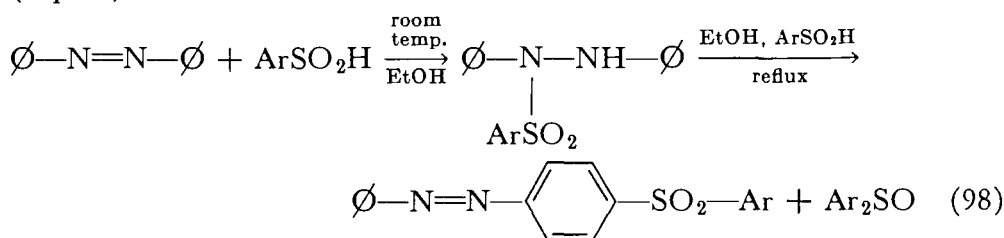
Although reactions of electron-deficient species such as $\text{R}-\ddot{\text{N}}:$ and $\text{R}_2\text{C}:$ with azo compounds have not been reported, certain cyclizations likely involve such a process. The cyclization of *o*-azidoazobenzenes to mesoionic benzotriazoles was mentioned in Chapter 10. The same type of product has also been reported from the reduction of an *o*-nitroazobenzene¹⁸² (Eq. 96). The oxidative cyclization of formazans to tetra-



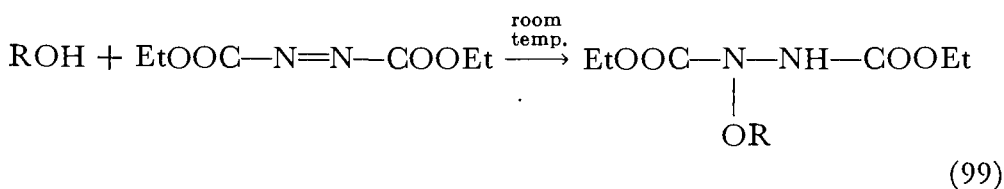
zolium salts⁵⁴ (Eq. 97) may be closely related.



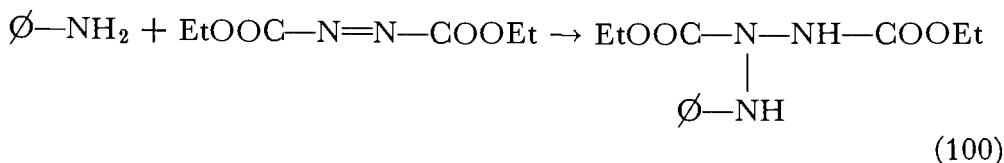
ELECTROPHILIC ADDITIONS There is a group of reactions that may for convenience be classified as electrophilic reactions of the azo grouping, in which various compounds bearing a potentially protonic hydrogen attached to a carbon, nitrogen, oxygen, or sulfur atom add across the $\text{N}=\text{N}$ bond. Ordinary azoalkanes and azobenzenes show little activity of this kind.¹⁶⁷ Azobenzene and some of its derivatives add sulfinic acids, however, to form sulfonyl hydrazines, which undergo reductive rearrangement when refluxed with excess sulfinic acid in ethanol to form sulfones¹⁸³ (Eq. 98).

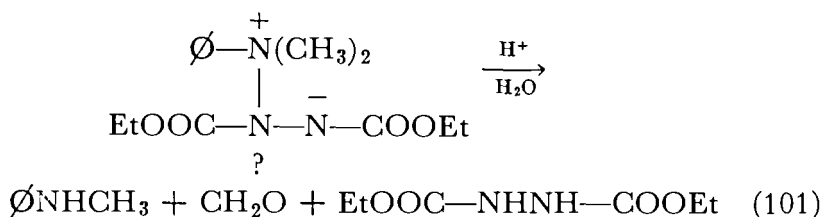


Most of the addition reactions have been established only for azodicarboxylic ester or its close derivatives; even azodibenzoyl is not as reactive. These reactions have been compared to diazonium coupling reactions. Alcohols and mercaptans form addition products with azodicarboxylic ester that are believed to be alkoxyhydrazine derivatives¹⁸⁴ (Eq. 99), which are of low stability and are decomposed by acids and

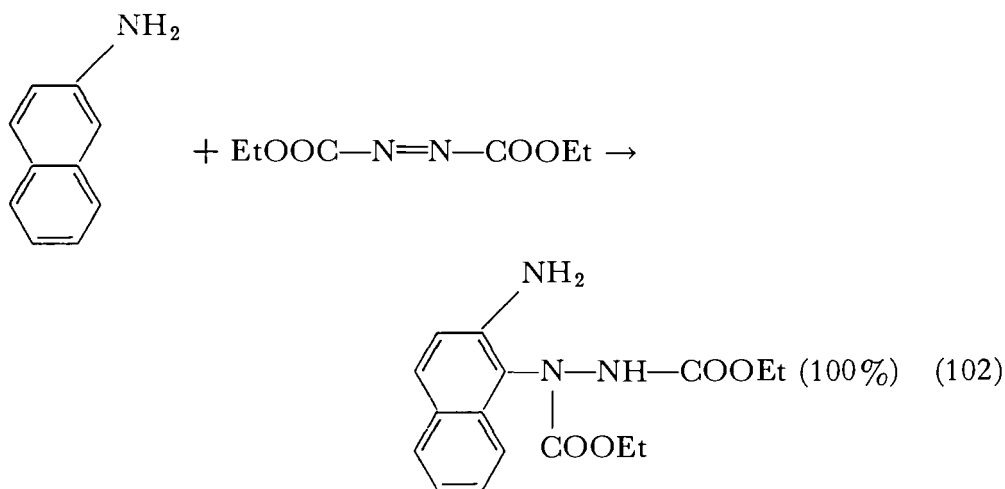


even such weak bases as potassium acetate. Aliphatic amines have not been observed to react with the azo group, but instead attack the carbonyl group in the usual fashion. Aromatic amines, however, form addition products readily, some of which appear to involve the formation of a nitrogen-nitrogen bond¹⁸⁵ (Eqs. 100, 101). In other cases, a ring carbon



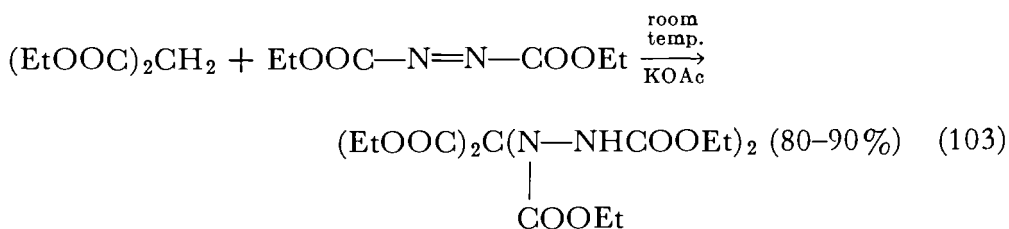


is attacked (Eq. 102). Indeed, such electrophilic attack by azodicarboxylic ester on aromatic rings is fairly general and is the basis of a useful



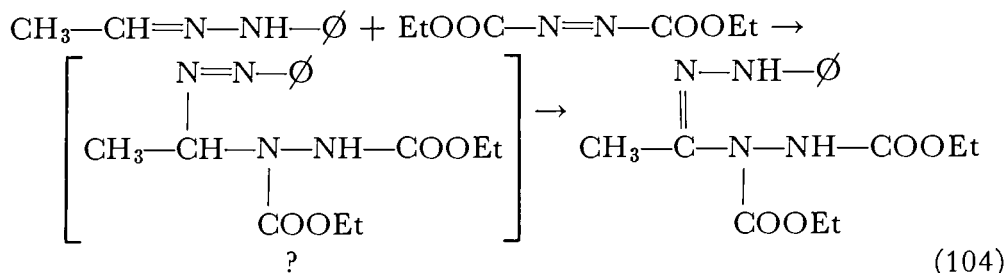
preparative method for arylhydrazines.¹⁸⁵ Benzoylazobenzene, in which the N=N bond must be one-sidedly polarized, has been shown to add to benzaldehyde phenylhydrazone; the products were originally thought to be tetrazanes,¹⁸⁶ but in view of the demonstration that azodicarboxylic esters attack the aldehyde carbon instead (see below), the tetrazane structure is probably incorrect.

Compounds with active methylene groups, such as malonic ester¹⁸⁷ and cyclohexanone,¹⁸⁸ add to azodicarboxylic ester so readily that both hydrogens become involved (Eq. 103).



Azodicarboxylic ester reacts with aldehydes to give hydrazides,^{189a} and in an analogous manner with their phenylhydrazones exothermically to

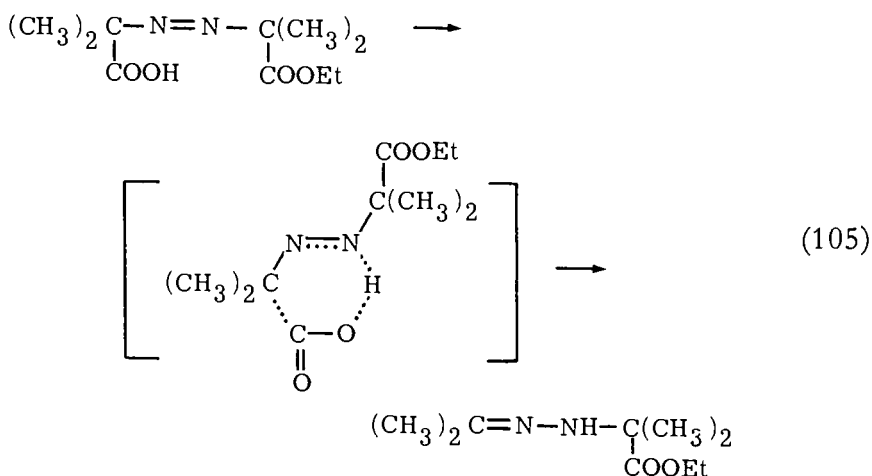
form hydrazidines ^{189b} (Eq. 104). Since this reaction fails with N,N-disubstituted hydrazones, it has been postulated that it must pass through a cyclic transition state in which the N-attached hydrogen of the hydrazone is transferred to the azo group at the same time as the new N—C bond



is formed, analogous to the reaction of azodicarboxylic esters with olefins. Ketone hydrazones have not been observed to react.

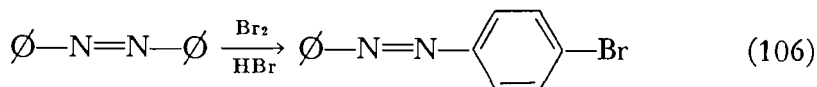
Diazoalkanes react with azodicarboxylic ester or diazocyanides to form azomethine imides ¹⁹⁰ (see pp. 245–246).

The azo group in many cases influences to a marked extent the chemical behavior of groups attached to it. A carboxyl group attached directly or α to an azo nitrogen is very unstable toward decarboxylation, and the free acids have not yet been isolated. Acidification of azodicarboxylate salts apparently gives rise to diimide itself in solution; its presence is inferred from the ability of the reaction mixtures to effect *cis*-hydrogenation of unsaturated compounds.¹⁹¹ The decarboxylation of α -azo acids is believed to occur by concerted intramolecular hydrogen transfer ¹⁹² (Eq. 105).

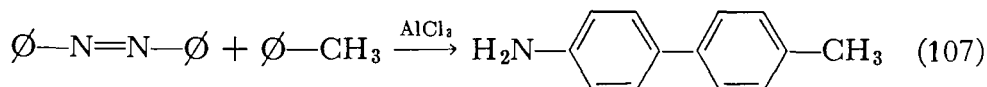


Substitution on azobenzene and its derivatives is not fully understood. Bromination is apparently immeasurably slow in the absence of hydrogen bromide, and the question inevitably arises of whether the observed products arise from azobenzene itself or from an addition product with hydrogen bromide ¹⁹³; the product isolated is *p*-bromoazobenzene (Eq. 106). Nitration also goes to the *para* position ¹⁹⁴; when that is blocked, as in

p,p'-dichloroazobenzene, oxidation to an azoxy compound occurs as well as *ortho* substitution.¹⁹⁵ A curious reaction has been reported between

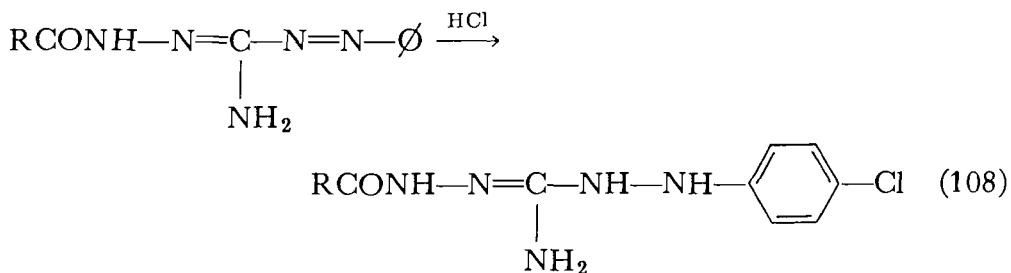


azobenzenes and toluene under Friedel-Crafts conditions; *p*-aminobiphenyls are produced¹⁹⁶ (Eq. 107).



FORMAZANS The special case of the formazans has been mentioned in the earlier parts of this chapter. Much of their chemistry⁵⁴ parallels that of other azo compounds, such as reduction to hydrazine derivatives,¹⁹⁷ and other reactions parallel the chemistry of hydrazines, such as acylation.¹⁹⁸ The most important individual reaction is certainly oxidation to tetrazolium salts. This is an easily reversible reaction, and a variety of reducing agents, particularly those found in biological systems, can accomplish regeneration of formazans. Because of this, tetrazolium salts have acquired a considerable importance in biological work as selective staining agents; the salts penetrate the cell and are reduced to the highly colored formazans at appropriate internal sites.

Among other unusual reactions of formazans may be mentioned that with hydrogen chloride,¹⁹⁹ which entails reductive chlorination, perhaps by way of addition to the N=N bond followed by halogen migration (Eq. 108). In other cases, acid has been observed to bring about hydroly-



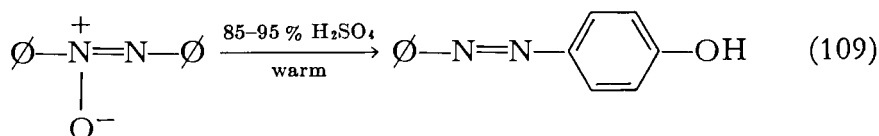
sis to a hydrazine and a diazonium salt²⁰⁰ or cyclization to a benzo-1,2,4-triazine.¹⁹⁸ Recent reviews⁵⁴ of formazan chemistry should be consulted for further information on this special subject.

C. Azoxy Compounds²⁰¹

The chemistry of azoxy compounds is largely concerned with certain rearrangements and reduction. Tautomerism with an amino nitrone structure, R—NH—N(O)=CR₂, has never been reported, although a cyclic representative of this structure is known.²⁰²

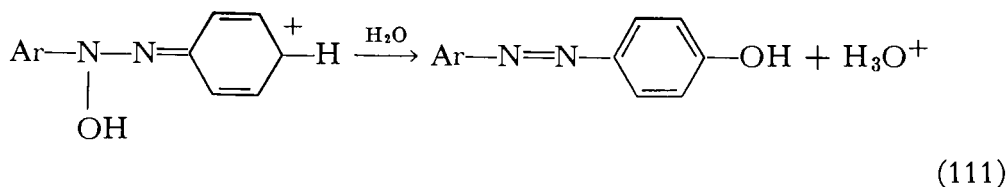
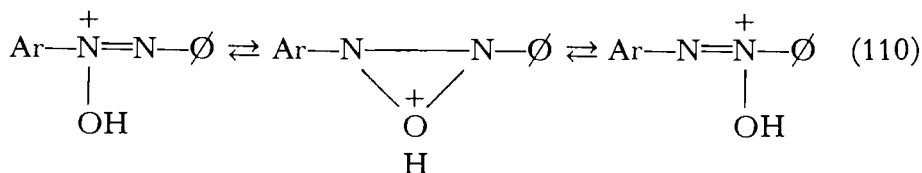
WALLACH REARRANGEMENT Azoxybenzenes can be rearranged to azo

phenols by exposure to sunlight, or by warming with strong acids (Eq. 109), when the transformation is known as the Wallach rearrangement. In the photolytic rearrangement, *ortho*-azo phenols are produced, the oxygen having migrated to the farther ring.²⁰³ With acid catalysis, the product is usually mostly *para*-azo phenol, accompanied by small amounts of *ortho*, some azobenzene, some amine, and polymer. Yields are best



when electron-withdrawing substituents are present.²⁰⁴ When one *para* position is blocked, the oxygen always migrates to the unsubstituted ring,²⁰⁵ usually taking the *para* position, but with *p*-methylazoxybenzene, substantial amounts of *o*-(*p*-tolylazo)phenol are formed. So general is the occurrence of the Wallach rearrangement that it has been proposed as a test for the azoxybenzene structure, a positive result being the formation of a product soluble in sodium carbonate solution.²⁰⁶

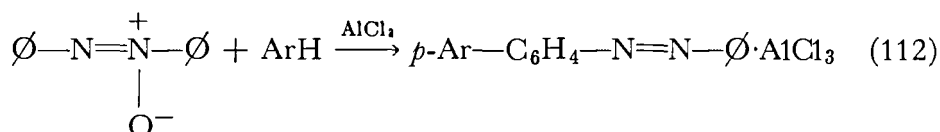
Experiments with O¹⁸ have shown that the migration of oxygen to a *para* position in the Wallach rearrangement is intermolecular, complete equilibration with the aqueous reaction medium taking place.^{205a} The *ortho*-azo phenols, on the other hand, arise without oxygen exchange with the solvent, and are presumably formed through a cyclic intermediate similar to that proposed for the photolytic rearrangement. The *para* rearrangement has been proposed to take place by protonation on oxygen, which may result in a symmetrical intermediate (Eq. 110), followed by attack on the ring by a water molecule^{205a} (Eq. 111). Indeed, N-to-N' migration of oxygen, presumably through such an intermediate, can be



detected as an intramolecular process accompanying the Wallach rearrangement.^{205c} Kinetic measurements show a dependence on acidity

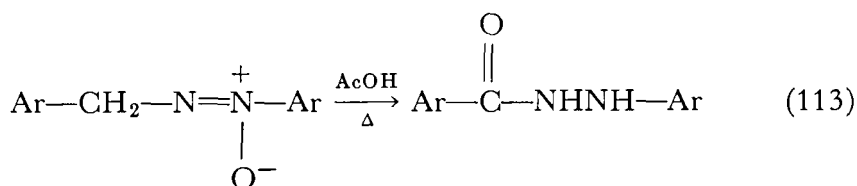
greater than that for monoprotection, however, and a dicationic intermediate has therefore been inferred.^{18a}

A Friedel-Crafts analog of the Wallach rearrangement occurs when azoxybenzene is treated with aluminum chloride in the presence of an aromatic hydrocarbon, an aryl group instead of a hydroxyl group entering a *para* position (Eq. 112). The resulting azo compounds are intensely

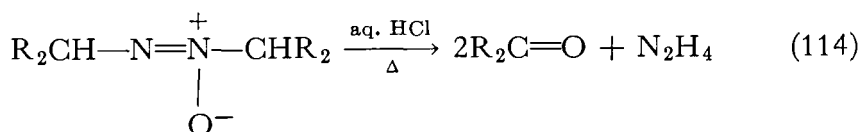


colored in the presence of aluminum chloride, and the reaction thus has value as a test for aromatic nuclei.¹⁹⁶

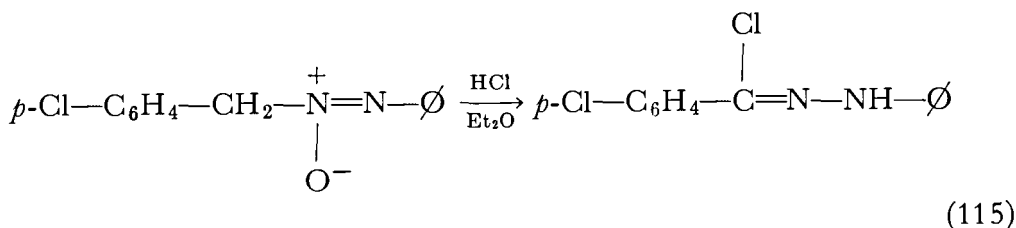
Treatment of azoxy compounds other than azoxybenzenes with acid leads to a different type of rearrangement. If a primary alkyl group is present, a hydrazide is formed^{9a} (Eq. 113); if two different but similar primary groups are present, the azoxy oxygen migrates to the closest alkyl group.²⁰⁷ When two secondary alkyl groups are present, ketones



and hydrazine are produced^{9a} (Eq. 114); their formation suggests initial dehydration to an azine followed by hydrolysis. When water is absent,

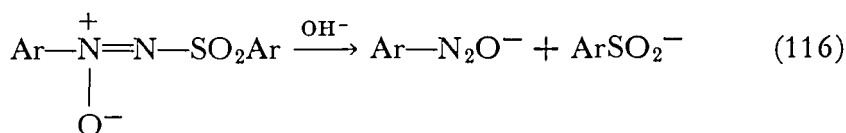


rearrangement of azoxy compounds carrying a benzyl group leads to hydrazonoyl chlorides (Eq. 115).¹ This fact clearly suggests that the rearrangements in aqueous solution pass through an analogous stage,

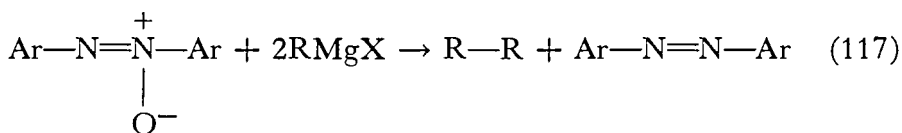


and therefore that the migration of oxygen is intermolecular.

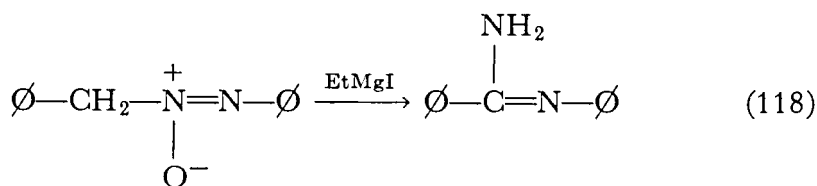
BASES Bases do not affect azoxy alkanes under mild conditions, but hot, concentrated alkali destroys them.^{9a} From azoxymethane, the products are cyanide ion and "volatile bases." Benzylic azoxy compounds are easily converted to oxidative dimers by exposure to strong base.¹⁰ Azoxy sulfones, however, are cleaved to form diazotate and sulfinate²⁰⁹ (Eq. 116).



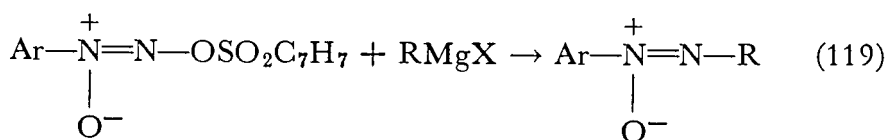
ORGANOMETALLIC REAGENTS Grignard reagents reduce azoxybenzenes to azobenzenes²⁰⁹ (Eq. 117), but N-benzyl-N'-phenyldiimide N-oxide undergoes rearrangement to an amidine²¹⁰ (Eq. 118). This reaction has been interpreted as a variety of Stevens rearrangement (see Chapter 2),



but it may equally well be an example of Robev's rearrangement of hydrazones to amidines if the first step is reduction to an azo compound, which would quickly tautomerize to benzaldehyde phenylhydrazone (see Chapter 9). Tosyloxy azoxy compounds undergo displacement of tosylate by

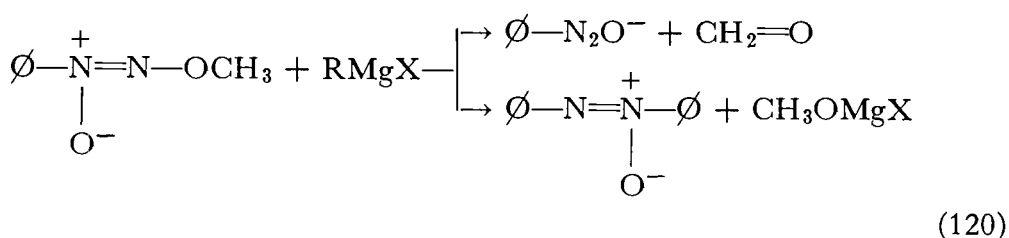


aryl when treated with one mole of Grignard reagent (Eq. 119), but phenyllithium forms a sulfone instead.^{211a} The corresponding methoxy

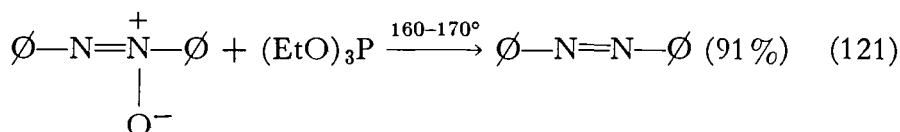


compounds are converted either to formaldehyde and diazotate, the

Grignard reagent evidently functioning as a base, or to azoxybenzenes ²¹¹ (Eq. 120).

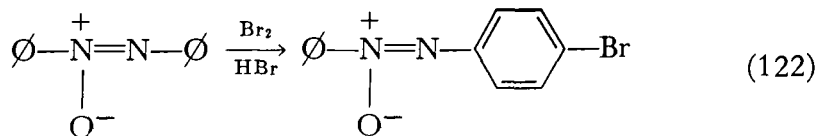


REDUCTION Reduction of azoxy compounds usually gives azo compounds, or can be stopped at that stage. Satisfactory reducing agents are ethyl phosphite ²¹² (Eq. 121), lithium aluminum hydride, ^{213, 214} and magnesium in ethanol.^{9a} With lithium aluminum hydride, *trans*-azobenzenes are always produced from either *cis* or *trans* azoxy compound ⁵²;



this has been attributed to intermediate formation of a hydroxyhydrazine derivative, in which free rotation about the N—N bond would be possible. Zinc dust ²⁰⁶ or stannous chloride ^{9a} give hydrazo compounds, whereas catalytic hydrogenation ^{9a} in acidic solution gives hydrazo compounds or amines.

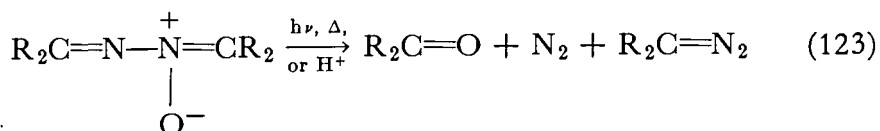
AROMATIC SUBSTITUTION Little has been published on substitution reactions of azoxybenzenes other than the observation that electrophilic attack occurs on the ring away from the oxygen (cf. the section on "Properties"). Azoxybenzene is said to be inert to bromine in the absence of hydrogen bromide, similar to azobenzene and nitrosobenzene,¹⁹³ from which it is inferred that it is an addition compound that actually reacts. The bromine then enters the *para* position of the ring away from oxygen (Eq. 122).



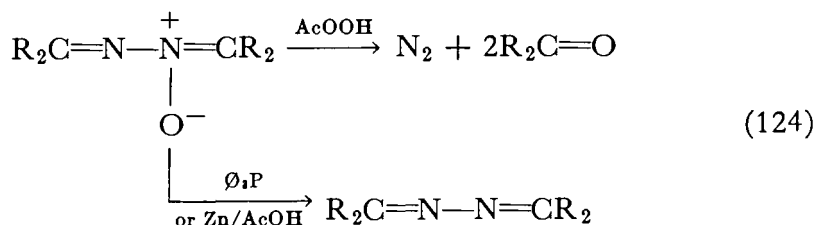
D. Azine Oxides

The chemistry of azine oxides has not been as thoroughly explored as that of the foregoing classes of compounds. Light, heat, or acid causes cleavage of the monoxides into nitrogen, ketone, and diazoalkane ^{13a}

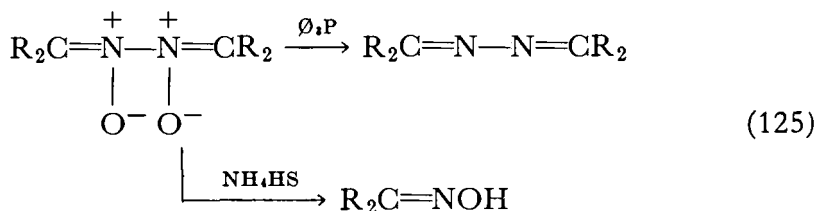
(Eq. 123). Peroxyacetic acid converts them to two moles of ketone,



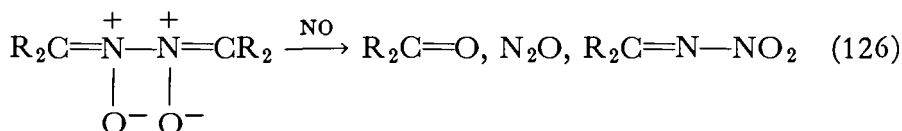
whereas reducing agents deoxygenate them to azines (Eq. 124).



Azine dioxides are also reduced to azines by triphenylphosphine, but



ammonium sulfide converts them to oximes instead ^{13b} (Eq. 125). Nitric oxide converts azine dioxides to ketone and nitrous oxide, or to nitrimines (Eq. 126). Since the azine dioxides give no detectable EPR signal up to 250°, the initial step in this reaction cannot reasonably be dissociation



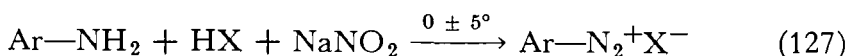
into $\text{R}_2\text{C}=\text{NO}$ radicals; it has been suggested that a nitroso nitrone, $\text{R}_2\text{C}=\text{N}(\text{O})-\text{NO}$, might be an intermediate.^{13b}

PREPARATIVE METHODS

A. Diazonium Salts

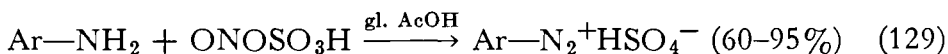
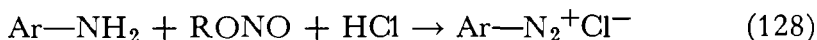
The preparation of diazonium salts in solution, usually accomplished by adding sodium nitrite to a solution of a primary aromatic amine in aqueous mineral acid solution (Eq. 127), has been described in great detail in numerous places,^{57, 92, 96, 101, 215} and we need not be further

concerned with the normal procedure here. A complication that occa-



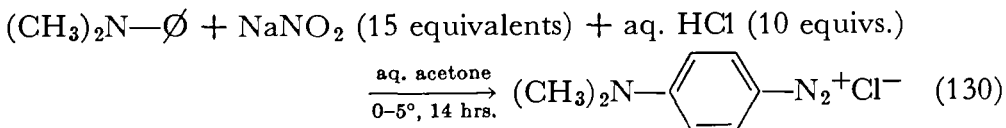
sionally arises is the precipitation of a fairly insoluble amine salt before diazotization is begun. Among the various ways in which this eventuality can be met may be mentioned use of an auxiliary solvent, usually alcohol or acetic acid. Frequently, however, the amine salts are sparingly soluble in these solvents, too. An alternative is to use a very hydrophilic anion, such as provided by ethanol- β -sulfonic acid.²¹⁶ The mechanism²¹⁷ of diazotization is discussed in Chapter 3.

The isolation of solid diazonium salts is easiest with the fluoborates, which usually precipitate from diazonium salt solution upon the addition of aqueous fluoboric acid; alternatively, the diazotization may be carried out using fluoboric acid as the initial acidifying agent.^{101, 218} In difficult cases, nitrosyl fluoborate in glacial acetic-propionic acid mixture has been used.⁸² For the preparation of more soluble salts, such as chlorides or bisulfates, contamination with inorganic salts is avoided by using alkyl nitrites instead of metal nitrites (Eq. 128); if alcohol is used as the solvent, the pure diazonium salt can be precipitated with ether. Alternatively, diazotization with nitrosylsulfuric acid in glacial acetic acid (Eq. 129)



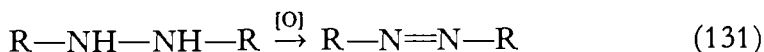
can be used.²¹⁹ Diazonium salts are also often isolated as sparingly soluble salts of large anions, especially metal complexes²²⁰ and arenesulfonate salts; the latter have the additional advantage of possessing greatly enhanced stability.^{57, 221}

Although there are several reactions by which diazonium salts are produced by cleavage of diazo compounds in acid solution, they do not seem to be of preparative significance. The direct introduction of the diazonium function by treatment of reactive arenes with a large excess of nitrous acid (Eq. 130) has preparative potential for the limited class of substrates to which it is applicable.²²²



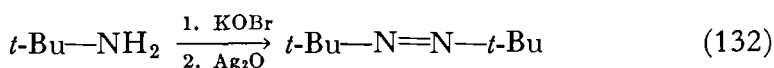
B. Azo Compounds

The most general route to azo compounds is oxidation of *sym*-disubstituted hydrazines (Eq. 131), for it can be accomplished equally well

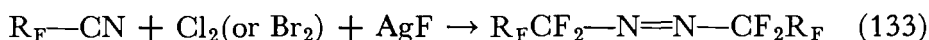


with aliphatic or aromatic compounds and with different or like groups. As oxidizing agents, hydrogen peroxide in aqueous ammonia, bromine,²²³ silver oxide,²⁷ amyl nitrite,¹⁴⁰ mercuric oxide,²²⁴ hypochlorous acid,²²⁵ nitric acid,²²⁶ and N-bromosuccinimide^{223b} may be mentioned.

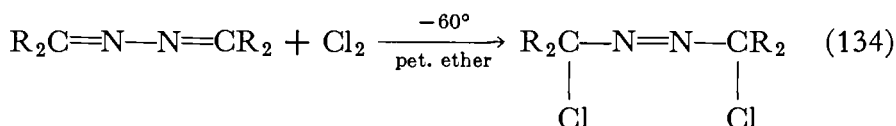
Oxidation of primary amines has been used in special cases to prepare azo compounds²²⁷; the reaction apparently requires a tertiary alkyl group for success (Eq. 132). Oxidation of hydrazones with lead tetra-



acetate is a preparative method for α -acetoxy azo compounds.²²⁸ Oxidation of nitriles to azo compounds appears to be confined to perfluoro compounds (Eq. 133), but in that area is a good method.¹⁴⁶ Chlorination of



azines (Eq. 134) is a distantly related reaction of preparative value for α -chloroazo compounds.²²⁹

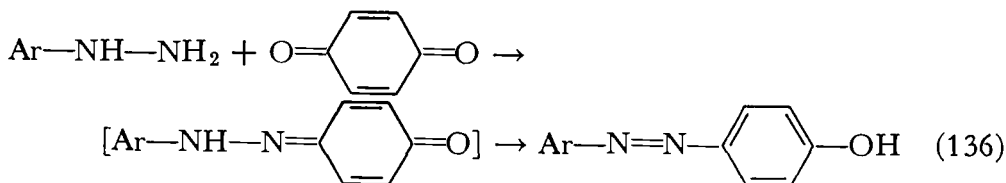


Hydrogenation of azines²³⁰ is often a good preparative method for primary or secondary alkyl azo compounds (Eq. 135), but suffers for

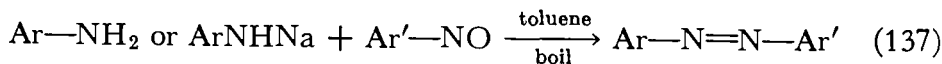


being somewhat erratic.

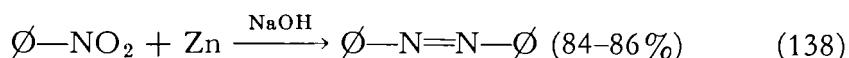
Diazo coupling, as discussed earlier in this chapter, is a technically valuable method for preparing azobenzene derivatives in which at least one ring bears an amino or hydroxy group. *p*-Hydroxyazobenzenes can also be prepared from quinones and arylhydrazines; the tautomerization from the hydrazone structure is spontaneous (Eq. 136). By the Japp-Klingemann coupling with carbanions,^{65, 67} or by coupling with organozinc compounds,⁶⁶ aryl alkyl azo compounds can be prepared (Eq. 9).



Condensation of nitroso compounds with primary amines (Eq. 137), known as the Mills reaction, leads readily to azobenzenes not available

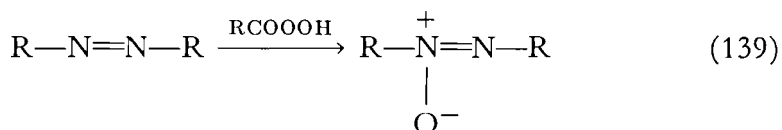


by diazonium coupling.²³¹ It is this reaction that is presumably responsible for the formation of azobenzenes in the reduction of aromatic nitro compounds²³² (Eq. 138) (see Chaps. 13 and 14).



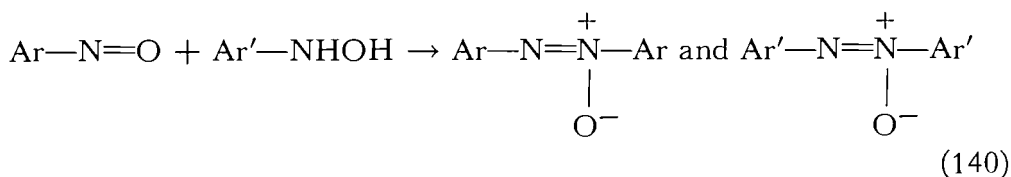
C. Azoxy Compounds

The most general preparative method for azoxy compounds is the oxidation of azo compounds with peroxyacetic or peroxybenzoic acid ^{10, 169, 213} (Eq. 139). This reaction preserves the geometrical configuration of the

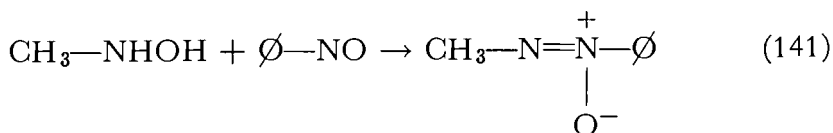


starting azo compound,^{52, 170} but has the disadvantage that unsymmetrical azo compounds may give rise to two structural isomers, or, worse still, to only the unwanted isomer. The corresponding hydrazines may be substituted for the azo compounds.¹⁶⁹

The condensation of nitroso compounds with monosubstituted hydroxylamines yields azoxy compounds readily, but unfortunately, equilibration may occur so that a pair of symmetrically substituted azoxy compounds may result (Eq. 140) instead of an intended unsymmetrical



one ²³³ (see Chapter 13). This is the usual behavior with aromatic participants, but nitrosobenzenes and alkylhydroxylamines give unsymmetrical products normally ^{9b} (Eq. 141). Purely aliphatic azoxy compounds can also be prepared by this reaction, using nitroso dimers; azoxycyclohexane, for example, is thus obtained in 47% yield.²³⁴ This

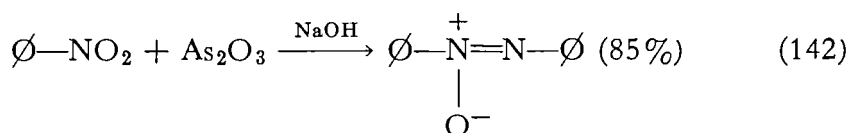


type of reaction can also be realized by air oxidation of aliphatic hydroxylamines.²³⁴

Azoxybenzenes prepared by this condensation are mostly *trans*, but some *cis* isomer is usually formed as well if alkali is present.^{51b} The position of the oxygen atom in an unsymmetrically substituted product is apparently determined by the actual nature of the groups, rather than by which group came from a nitroso or hydroxylamine starting material, for it appears probable that the condensation passes through an intermediate dihydroxyhydrazine, in which the nitrogens are similar.²³⁵

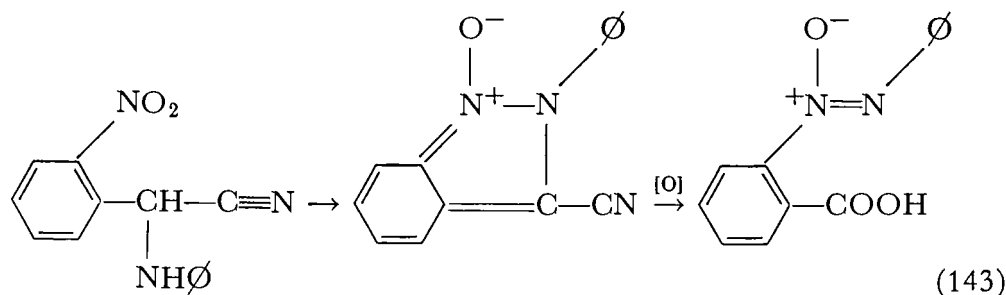
Hydrogenation of some cycloaliphatic nitroso dimers over a palladium catalyst has given moderate to good yields of azoxyalkane.²³⁴

Reduction of nitrobenzenes under properly chosen conditions gives azoxy compounds (Eq. 142). Reduction in part to nitrosobenzene, in part to phenylhydroxylamine, probably occurs, followed by condensa-

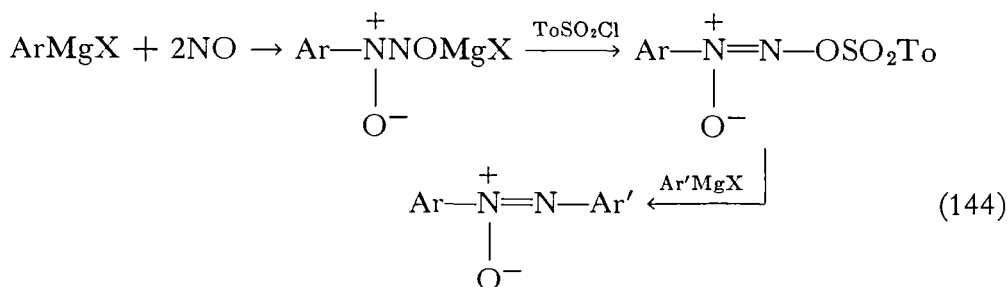


tion.²³⁵ The successful reducing agents are all more or less basic and include arsenite,²³⁶ sodium borohydride (usually very slow),²³⁷ sodium methoxide,²³⁵ phosphine,²³⁸ and electrolysis.²³⁹

The preparation of azoxy compounds by the oxidative cleavage of indazole oxides⁵³ (Eq. 143) was mentioned earlier in connection with the identification of structurally isomeric azoxy compounds. The required indazoles are prepared from α -anilino-*o*-nitrophenylacetonitriles, and the overall procedure is probably too cumbersome to be of preparative value except in special cases.



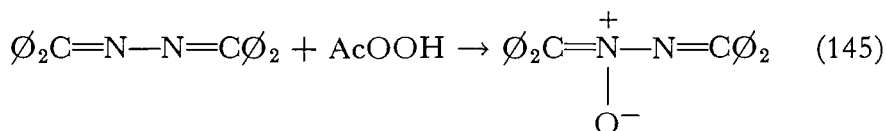
The reaction of Grignard reagents with tosyloxy or alkoxy azoxy compounds (Eq. 119) is a potentially useful synthetic method for other azoxy compounds, for the substrates are prepared fairly simply by treating an aryl Grignard reagent with two equivalents of nitric oxide (Eq. 144), and then acylating (or alkylating) the resulting nitrosohydroxylamine



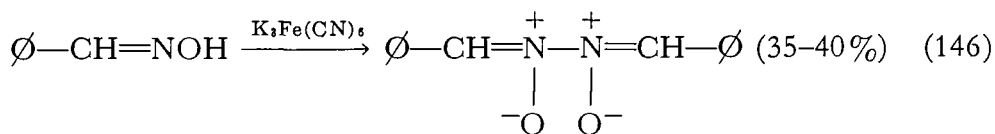
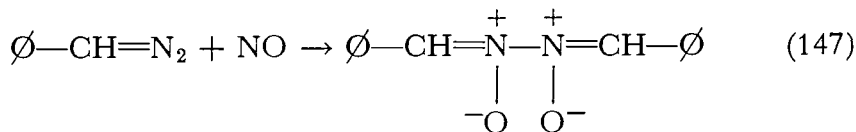
magnesium salt.²¹¹ The analogous reaction of fluoroazoxy compounds, ArN(O)NF , with Grignard reagents in some instances also affords azoxy compounds in preparatively useful yields.¹²

D. Azine Oxides, Formazans, Nitrosazones, and Nitrazones

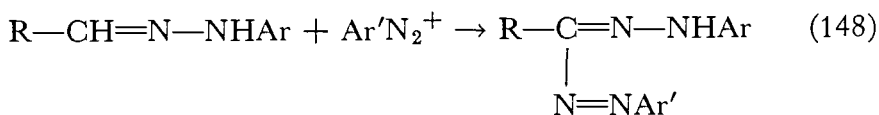
The only reported preparative method for azine monoxides is the reaction of azines with peroxy acids ^{13a} (Eq. 145). The monoxides have



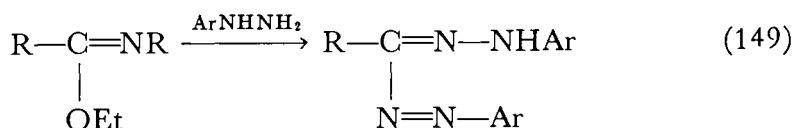
not been successfully oxidized further to the N,N'-dioxides, which must instead be prepared by the oxidation of oximes with ferricyanide or oxides of nitrogen (Eq. 146), or by the reaction of diazo compounds with nitric

oxide ^{13b} (Eq. 147).

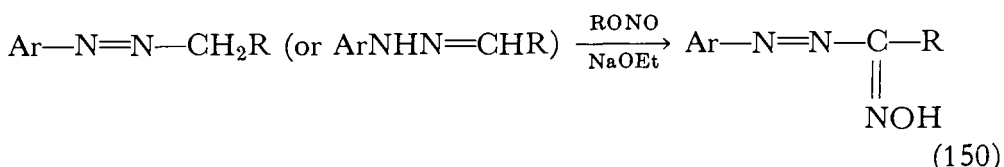
Formazans are in general prepared ⁵⁴ by a coupling reaction between aldehyde arylhydrazones and diazonium salts (Eq. 148), or by the forma-



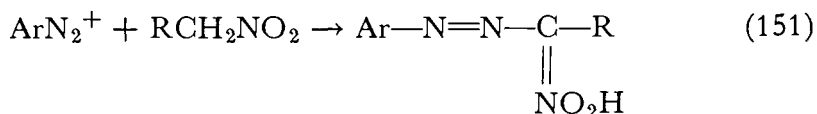
tion and oxidation of hydrazidines by the interaction of arylhydrazines with sufficiently reactive derivatives of the carboxyl group, such as imidate esters (Eq. 149).



Nitrosazones⁵⁵ are prepared by the nitrosation of azo compounds or the tautomeric hydrazones (Eq. 150). Nitrazones⁵⁵ are prepared by the



coupling of diazonium salts with primary nitroalkanes (Eq. 151) or the



oxidation of nitrosazones with excess alkyl nitrite; the direct nitration of benzaldehyde phenylhydrazone to a nitrosazone has also been reported.^{55a}

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*chapter
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Other Compounds with Chains of Three or More Nitrogens

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NOMENCLATURE

Chains of nitrogen atoms joined only by single bonds are named by means of a prefix corresponding to the number of nitrogen atoms in the chain and the generic route “-azane”; $\text{H}_2\text{N—NH—NH—NH}_2$ is thus called “tetrazane.” The chains are numbered in the same way as carbon chains. Unsaturation is indicated the same way as in carbon chains, by changing the last syllable to -ene, -diene, etc.; $(\text{CH}_3)_2\text{N—N=NNHEt}$ is thus called 1,1-dimethyl-4-ethyl-2-tetrazene. This system is sometimes extended to chains of only two nitrogens, allowing azo compounds to be

named alternatively as diazenes. The names "prozane" and "buzane" instead of triazane and tetrazane were originally proposed by Curtius, but their use has long since died out. Names ending in "-azone" were once widely used for some types of unsaturated nitrogen chains, but their meaning degenerated into such ambiguity that they, too, have long ago been abandoned. The word "tetrazene" is also sometimes used for the explosive, 4-amidino-1-nitrosaminoamidino-1-tetrazene.

GENERAL REMARKS ²

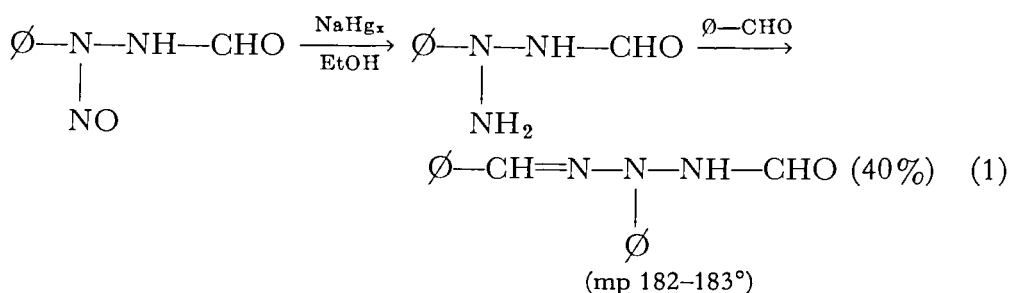
The considerable variety of compounds of different structural types, each with more or less distinct chemistry, evokes a departure from the form of the other, more homogeneous, chapters. Furthermore, the literature concerning most of the types is quite limited. In view of this state of affairs, the properties, reactions, and preparation will be dealt with together in each case, and the chapter will be subdivided according to length and degree of unsaturation of the nitrogen chains.

It appears in general that chains of three or more nitrogens are easily broken by elimination of an amine when a hydrogen is present on at least one nitrogen and by homolytic dissociation when fully substituted. Some degree of stabilization seems to be conferred by unsaturation, either $N=N$ or $C=N$, and the known examples of chains of three or more nitrogens are almost all unsaturated in one way or another. Although some structural types that might be stable remain unrepresented because no feasible synthetic route has been contrived, others remain unknown in spite of a variety of fully credible preparative routes. Such structural types are therefore inferred to be inherently unstable. The types taken up in this chapter are those of which at least one isolable example has been reported.

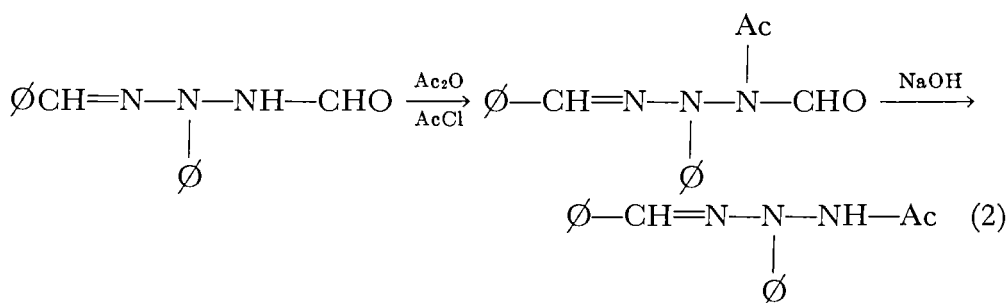
TRIAZANES

Very few triazanes have been reported, and for many of them the supporting evidence is inadequate; the analyses in several instances are not acceptable by present-day standards.

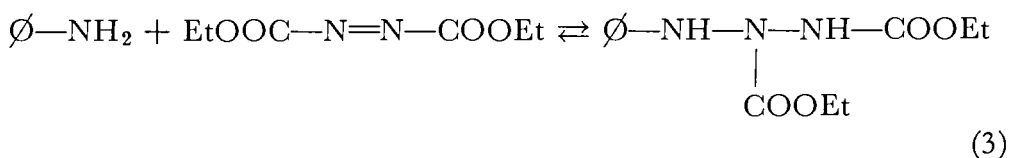
1-Acyl-2-phenyl-3-benzylidenetriazanes have been prepared by the reduction of N' -nitroso- N' -phenyl hydrazides with sodium amalgam and treatment of the reaction mixture with benzaldehyde ³ (Eq. 1). The intermediate 1-acyl-2-phenyltriazanes can be handled in solution, but are too unstable to isolate and easily revert to the original hydrazide. The benzylidene derivatives are colorless, crystalline substances, soluble in



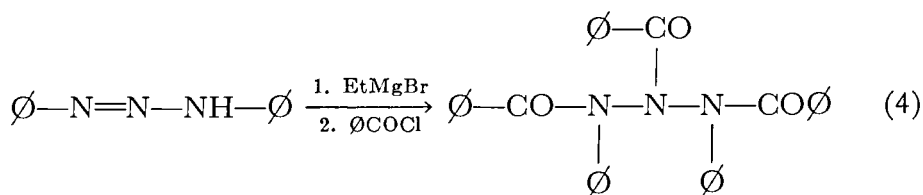
aqueous alkali, from which they are reprecipitated unchanged by acid. Hot, dilute hydrochloric acid breaks up the molecule into benzaldehyde and phenylhydrazine. The formyl member has been acetylated by a mixture of acetic anhydride and acetyl chloride; alkali removes the formyl group from the product, leaving the acetyl derivative (Eq. 2).



Dicarboethoxytriazanes, such as 1-phenyl-2,3-dicarboethoxytriazane, mp 138° , have been obtained in some instances by the addition of amines to azodicarboxylic ester ⁴ (Eq. 3). They decompose easily into the original reactants.



1,3-Diphenyl-1,2,3-tribenzoyltriazane, mp $160\text{--}161^\circ$, has been obtained by treating diphenyltriazene with excess Grignard reagent, which acts as a reducing agent, and benzoylating the reaction mixture ⁵ (Eq. 4). Another triazene, guanylcarbamyltriazene, has also been reduced to



what may have been a triazane; the unstable product was obtained only in solution and was easily oxidized back to the triazene.⁶

The reduction of nitrosohydrazine derivatives offers a logical route to triazanes, yet it has had little success, and except for the nitroso hydrazides, even the mildest reduction cleaves off the nitroso group. All attempts to prepare trimethyltriazane by reducing trimethylnitrosohydrazine have failed, for example; only products of N—N cleavage were obtained.⁷ Several simple triazanes were originally reported to have been obtained by reduction of the compounds resulting from the condensation of N-nitrosophenylhydrazine with acetaldehyde ammonia (α -hydroxyethylamine), but the entire series was subsequently shown to have been misidentified.⁸

TRIAZENES

The triazenes are certainly the best known of all the chains of three or more nitrogens, other than azides. The diaryl derivatives, such as 1,3-diphenyltriazene (diazaminobenzene), mp 98–99°, are fairly stable substances, as are the 1-aryl-2,2-dialkyl derivatives, many of which have been distilled at temperatures as high as 158°/0.7 mm.⁹ The 1-aryl-3-alkyl derivatives, such as 1-phenyl-3-methyltriazene, mp 37–37.5°, are somewhat less stable, and generally decompose below 100°. The only simple monoaryl triazene, 1-phenyltriazene,¹⁰ mp 50°, is extremely unstable; more complicated monoaryltriazenes, such as 1-(1-anthraquinonyl)-triazene, are known, however.¹¹ Purely aliphatic triazenes are represented by 1,3-dimethyltriazene, a colorless, water-miscible liquid that boils with decomposition at 92°; it explodes on rapid heating.¹²

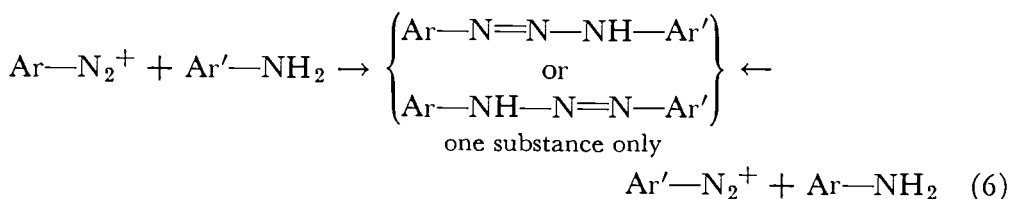
Disubstituted triazenes are distinctly acidic and usually form easily isolated cuprous salts. The triazenes evidently possess some basic character also, for they are decomposed by mineral acids, in some instances extremely easily. Some 1-aryl-3,3-dialkyltriazenes form isolable picrates, however.

1,3-Disubstituted triazenes are obviously capable of tautomerism (Eq. 5), but separate tautomers of unsymmetrical examples have not yet



been conclusively identified. It is true that some 1,3-diaryl triazenes have been obtained in different forms, but these could as well be geometrical isomers or polymorphic forms on the basis of the available evidence.¹³ Indeed, the molecular weights of such triazenes indicate that they form hydrogen-bonded aggregates, in which tautomeric proton

transfer would be so easy that it is doubtful that separate tautomers could ordinarily be isolated.¹⁴ Attempts to prepare isomeric 1,3-diaryl triazenes have always given the same product¹⁵ (Eq. 6). The geometrical configuration of triazenes is probably commonly *trans*; dipole moments do



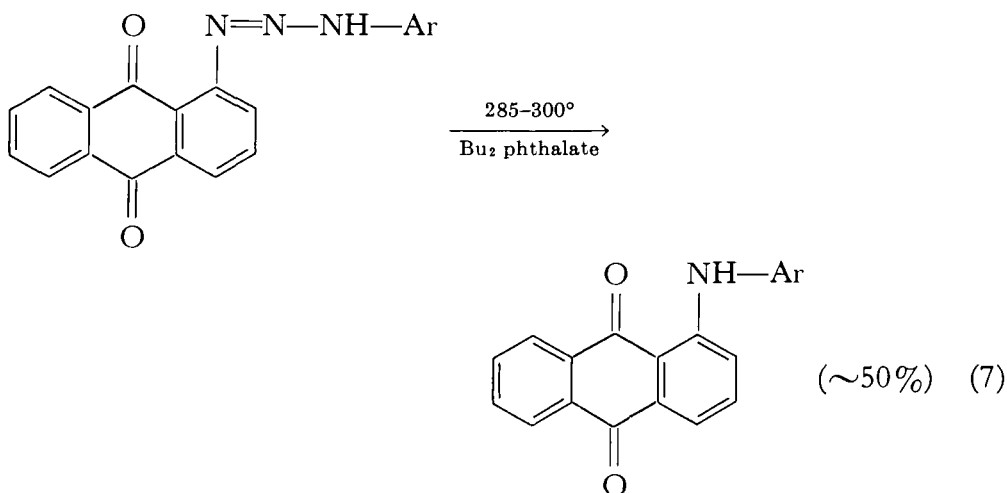
not conclusively settle the point.¹⁶

The diaryl triazenes are commonly light yellow or golden when pure, but traces of the isomeric aminoazobenzene, which are difficult to remove, may make the color darker.¹⁷ 1-Aryl-3,3-dialkyl triazenes are likely to be yellowish, but aryl alkyl triazenes, as well as phenyltriazene and 1,3-dimethyltriazene, are colorless. The $\text{N}=\text{N}$ stretching frequency of triazenes has been identified with absorption at $1410\text{--}1418\text{ cm}^{-1}$ in the infrared,¹⁸ and thus resembles that of other azo compounds. Absorption in the near ultraviolet is generally strong and usually appears as more than one band.¹⁶

Alkylidene triazenes, $\text{R}_2\text{C}=\text{N}-\text{N}=\text{N}-\text{R}$, are known.¹⁹

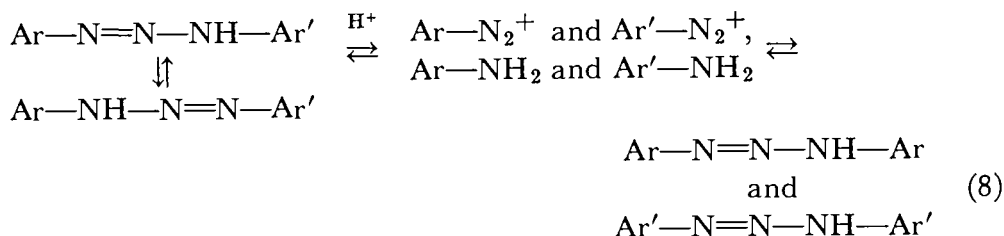
Although triazenes are fairly stable to heat, most of them decompose at temperatures below 300° . Nitrogen is then lost, and amines are formed²⁰ (Eq. 7).

Acids generally decompose triazenes into amines and diazonium salts



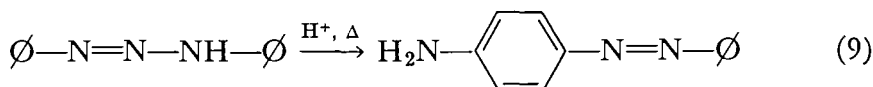
or their further transformation products; with aryl triazenes, this is simply the reversal of the reaction by which they are most readily made. Owing to the tautomeric equilibrium in unsymmetrical 1,3-diaryl triazenes, both

possible amines and both possible diazonium salts are formed (Eq. 8). Recombination can occur if the medium is not strongly acid, and can,



of course, lead to a pair of symmetrical triazenes as well as the original one.²¹

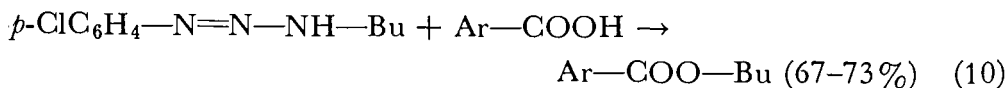
Acid also causes a slower rearrangement to an aminoazobenzene structure²² (Eq. 9); this almost certainly occurs to a significant extent through the aforementioned cleavage, followed by slow electrophilic attack on the ring of the amine. The *para* isomer is generally formed



unless the *para* position is blocked. This rearrangement is definitely accelerated by the presence of free aromatic amine,²³ an effect that is ascribed to a concerted process in which the triazene N—N bond is cleaved at the same time the new N—C bond is formed in a kind of nucleophilic displacement on nitrogen.²⁴

Homolytic decomposition of triazenes can also be catalyzed by acids. Acetic acid or hydrogen chloride are the most effective acids, and the reaction is believed to be actually that of the diazonium acetate or chloride first formed.²⁵ Arylation of olefins, coumarin, etc. is thus accomplished by aryltriazenes. 1,3-Diphenyltriazene has been observed to catalyze the polymerization of acrylonitrile.²⁶

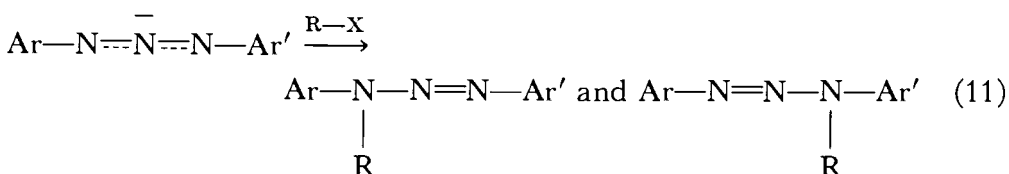
Triazenes may act as useful alkylating agents through the acid-catalyzed cleavage reaction if temperatures below that at which homolytic cleavage is favored are used. 1-Phenyl-3-methyltriazene has been claimed to rival diazomethane as a methylating agent, and 1-*p*-chlorophenyl-3-butyltriazene has been used for the butylation of not only carboxylic acids, but also phenols, mercaptans, and some alcohols.²⁷



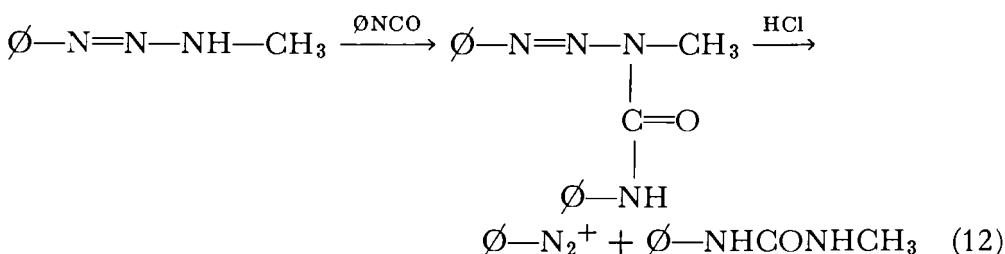
Presumably the alkanediazonium ion, identical to that obtained from the corresponding diazoalkane, is an intermediate.

In alkaline solution, disubstituted triazenes can be alkylated. The anion of an unsymmetrical triazene is, of course, an ambident system

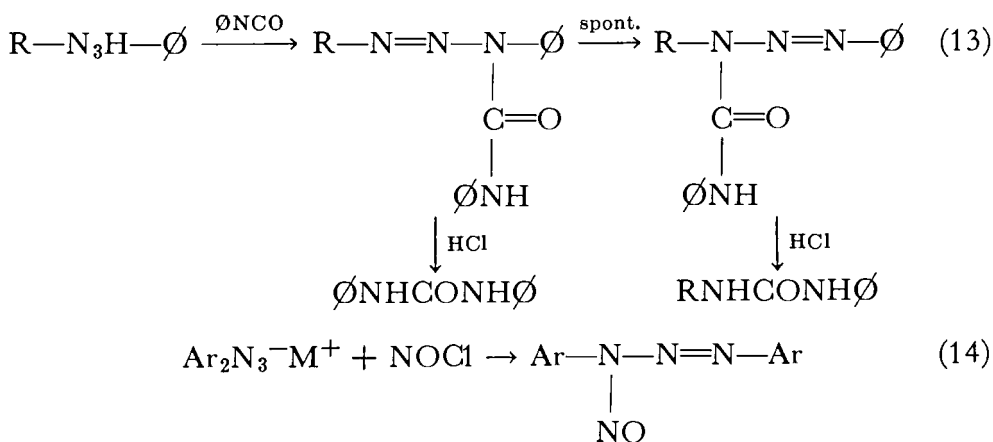
and can become alkylated at either terminal nitrogen. Both isomeric products have, indeed, been detected from such a reaction.²⁸



The common acylating agents attack mono- and disubstituted triazenes normally to give monoacyl derivatives; phenyl isocyanate has been particularly widely used.^{10, 29} Since only one of the theoretically possible



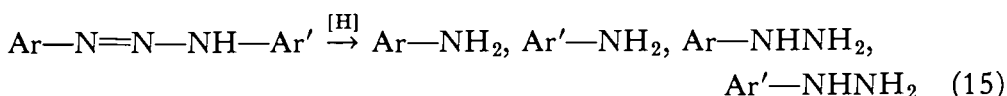
isomeric acylation products is usually obtained, acylation was at one time believed to be a reaction peculiar to the saturated nitrogen and thus diagnostic of the tautomeric constitution. This hypothesis was vitiated when it was shown for phenylcamphoryltriazene that spontaneous migration of acyl group occurs on standing.³⁰ Nitrosation is accomplished by the reaction of triazene salts with nitrosyl chloride (Eq. 14); the nitrosotriazenes are isomeric with the diazoanhydrides (Chapter 11) and not



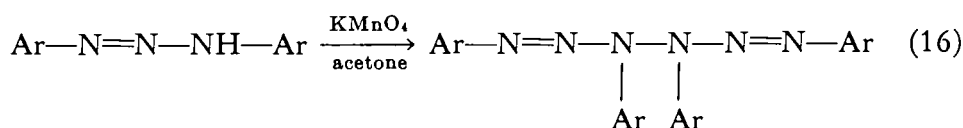
identical with them.³¹

Diazonium salts couple with disubstituted triazenes to form pentazadienes, but the reaction does not occur readily with diaryl triazenes except in alkaline solution (see Pentazadienes).

Triazenes are readily reduced, but all attempts to stop the reduction at the triazane stage have failed; amines and hydrazines are the only products isolated ³² (Eq. 15). Oxidation of disubstituted triazenes with



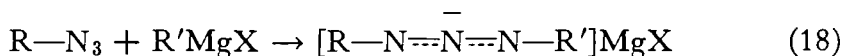
permanganate produces hexazadienes ³³ (Eq. 16).



Triazenes are prepared either by the coupling of diazonium salts to primary or secondary amines ^{9, 22, 34} (Eq. 17), or by the reaction of azides

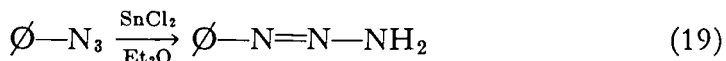


with Grignard reagents ^{32, 35} (Eq. 18). Only the latter reaction, of course,



is suitable for preparing dialkyl triazenes. Releasing the acid-sensitive triazenes from their magnesium salts is a delicate operation, and it is usually advisable first to prepare the more stable cuprous salts by treatment with ammoniacal cuprous salt solution. In the instance of the especially sensitive compound dimethyltriazene, the free substance was eventually obtained by grinding the cuprous derivative with diphenyltriazene ¹²; even ammonium chloride was too acidic to use.

Monosubstituted triazenes are the most difficult to prepare. Reduction of an azide to a triazene, which is only exceptionally successful, is exemplified by the preparation of phenyltriazene ¹⁰ (Eq. 19). Coupling



of diazonium salts to ammonia cannot usually be stopped short of pentazadiene formation, but there are some exceptions, such as the preparation of 1-anthraquinonyltriazene. ¹¹

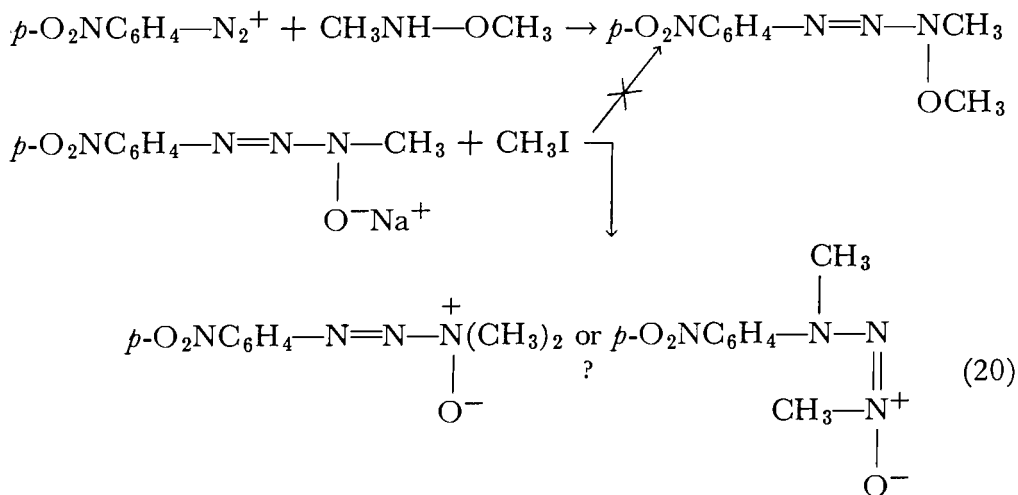
HYDROXYTRIAZENES AND TRIAZENE OXIDES

Disubstituted hydroxytriazenes, $\text{R}-\text{N}=\text{N}-\text{N}(\text{OH})\text{R}$, are known in moderate variety, but only a few monosubstituted derivatives are known. All the reported examples are crystalline solids acidic enough to dissolve in aqueous alkali. 1-Phenyl-3-methyl-3-hydroxytriazene, mp 69–70°,

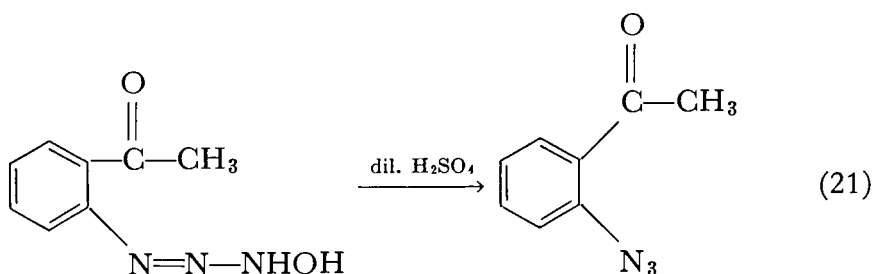
is colorless,³⁶ whereas 1,3-diphenylhydroxytriazene, mp 127°, is lemon yellow,³⁷ and 1-(1-anthraquinonyl)-3-hydroxytriazene is bright red.³⁸ The alkali metal salts are generally deeply colored, in many cases blue to violet. Chelate complexes are formed readily with copper, cobalt, nickel, or iron salts.³⁹ Values of 9.98 to 12.7 have been reported^{37b} for pK_a of various diaryl hydroxytriazenes. The hydroxytriazene structure has been arbitrarily assumed for the foregoing substances for convenience, but the possibility of tautomerism with the triazene N-oxide structure is evident. In fact, the infrared spectrum of the ¹⁵N-labelled 1,3-diphenyl compound indicates it to have the triazene oxide structure with chelate hydrogen bonding.^{37c}

The triazene oxides, $R-N=N-N(O)R_2$, which represent a further degree of substitution of the same oxidation state, are neutral, crystalline substances, soluble in common organic solvents, but insoluble or nearly so in water. 1,3-Diphenyl-3-methyltriazene-1-oxide, mp 72° , is sulfur yellow and volatile with steam⁴⁰; other examples are colorless to yellow.

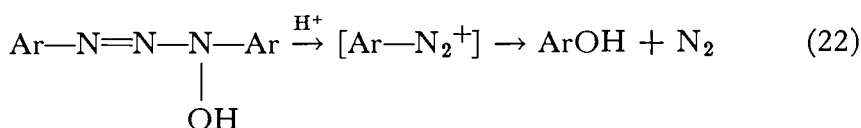
The salts of hydroxytriazenes react with alkyl halides to form alkyl derivatives whose structure has not been established with certainty. 1-*p*-Nitrophenyl-3-methyl-3-hydroxytriazene, for example, can be methylated with methyl iodide and sodium hydroxide to give a yellow-brown product, mp 142°, isomeric with 1-*p*-nitrophenyl-3-methyl-3-methoxytriazene, mp 66°, whose structure is reasonably certain by virtue of its synthesis from O,N-dimethylhydroxylamine and *p*-nitrobenzenediazonium chloride ⁴¹ (Eq. 20).



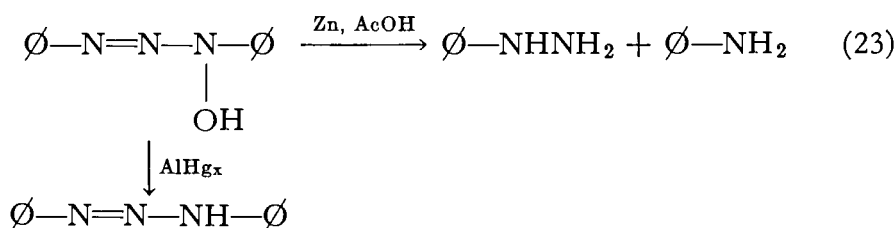
Monosubstituted hydroxytriazenes lose water very easily to become azides (Eq. 21); acylating agents and even dilute acids accomplish the change.^{38, 42} Disubstituted hydroxytriazenes and triazene oxides are



apparently cleaved by strong acids into hydroxylamines and diazonium salts or their decomposition products (Eq. 22), analogously to the acid cleavage of triazenes. Reduction in acidic medium is commonly accom-

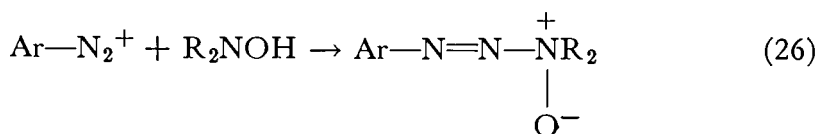
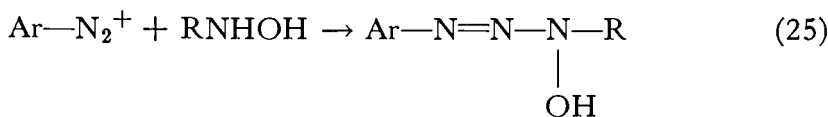
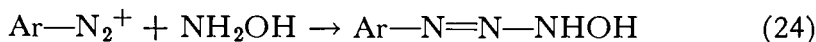


panied by such cleavage (Eq. 23), and the yields of triazene may be small.^{37, 40} Reduction to triazenes is better accomplished with aluminum



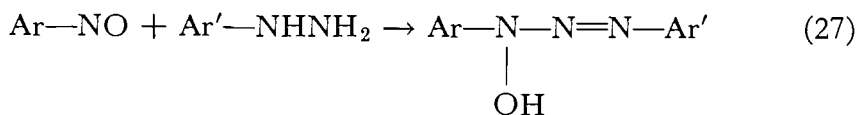
amalgam.

Hydroxytriazenes and triazene oxides can be prepared in considerable variety by coupling of diazonium salts with hydroxylamines^{36, 38, 41} (Eqs. 24–26). The reaction of nitrosobenzenes with arylhydrazines or

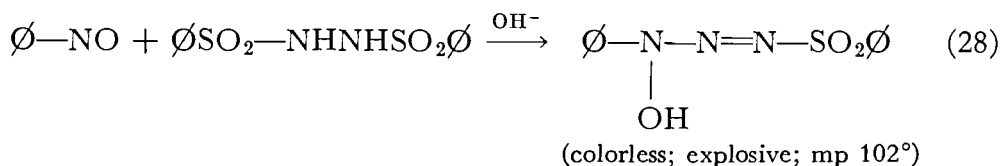


N-aryl-N-alkylhydrazines somewhat less obviously gives rise to hydroxytriazenes or triazene oxides (Eq. 27); the reaction is apparently of preparative value^{36, 40} (but cf. Chapter 13!). An initial aldol-like hydroxytria-

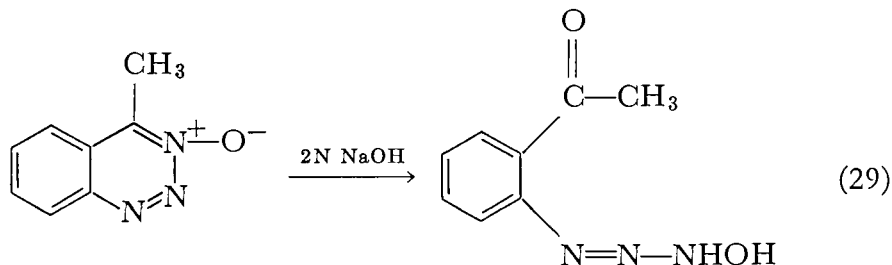
zane is presumably dehydrogenated by air or excess nitroso compound.



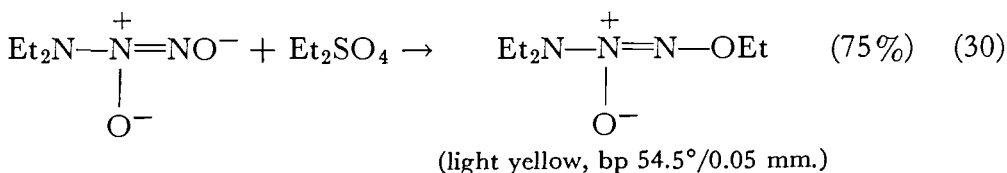
Sulfonyl triazene oxides have been prepared by the closely related reaction of nitrosobenzenes with N,N' -dibenzenesulfonylhydrazine in the presence of alkali ⁴³ (Eq. 28); elimination of sulfinate accomplishes the



necessary oxidation. A reaction of less general application is the cleavage of benzotriazine oxides with alkali ⁴² (Eq. 29).

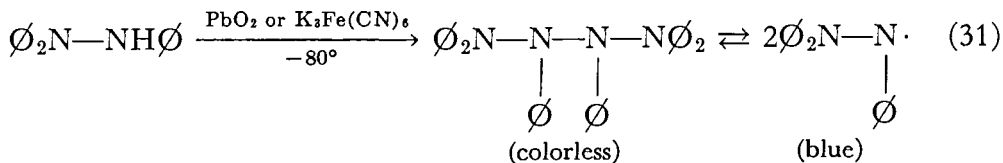


A different class of triazene oxide has been obtained from ethylation of the product from the reaction of nitric oxide with secondary amines ⁴⁴ (Eq. 30).



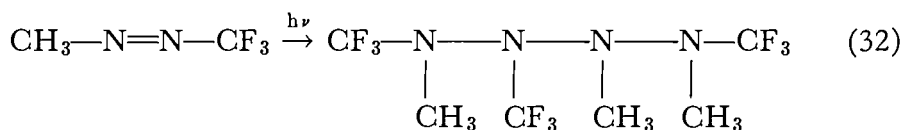
TETRAZANES

A number of fully substituted tetrazanes and several partially substituted tetrazanes are known. Hexaphenyltetrazane is formed by oxidation of triphenyl hydrazine (Eq. 31); it is a white solid when very cold,



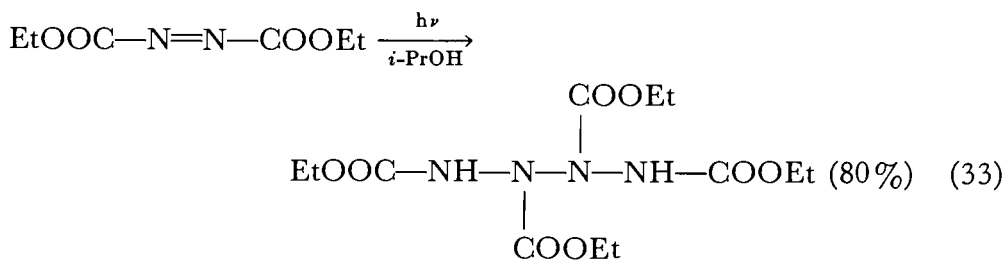
but green at room temperature, and dissociates reversibly in solution into blue triphenylhydrazyl radicals.⁴⁵ Many other hexaaryltetrazanes have been reported, and nearly all are highly dissociated into hydrazyl radicals, some, such as tripicrylhydrazyl, apparently even in the solid state. For this reason, these compounds are referred to as hydrazyls at least as often as they are called tetrazanes (cf. Chapter 9). 1,2,3,4-Tetraaryl-1,4-diacyltetrazanes, however, dissociate very little. The dissociation of 1,1,4,4-tetraaryl-2,3-dibenzoyltetrazane has been thoroughly investigated from both equilibrium and kinetic standpoints⁴⁶; both rate and equilibrium constants obey the Hammett linear free energy relation ($\rho = -1.52$ for equilibrium), and there is a linear relation between entropy and enthalpy.

1,2,4-Trimethyl-1,3,4-*tris*(trifluoromethyl)tetrazane, bp 75°/135 mm., is formed by photolysis of methyltrifluoromethyldiimide ⁴⁷ (Eq. 32); it apparently does not dissociate detectably under ordinary conditions.



A partially unsubstituted tetrazane has been reported to result from the oxidation of 1-hydrazinophthalazine by oxygen in the presence of ferrous ion; the tetrazane forms a deep red, presumably chelate, complex with ferrous ion.⁴⁸

1,2,3,4-Tetracarboethoxytetrazane, mp 80°, has been reported to result from reductive coupling of azodicarboxylic ester ⁴⁹ (Eq. 33). Above its melting point, this tetrazane apparently dissociates into hydrazyl



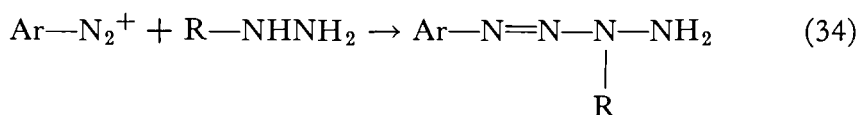
radicals, for products corresponding to their disproportionation are then found.

A number of alkylidene tetrazanes have been reported in the older literature as products of the oxidation of arylhydrazones or of the addition of arylhydrazones to azo compounds. More recent evidence, however, makes it appear very unlikely that any of these products were tetrazanes (see Chapter 9 for references and further discussion).

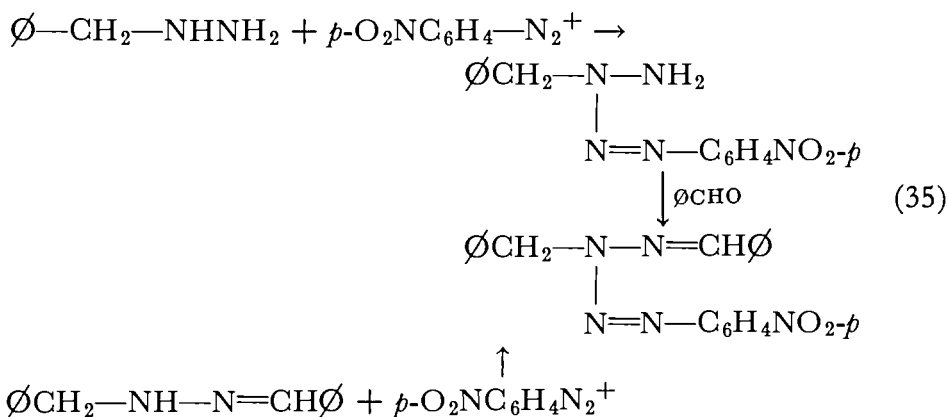
TETRAZENES

Both 1-tetrazenes, $R-N=N-NRNR_2$, and 2-tetrazenes, $R_2N-N=N-NR_2$, are known in some variety in both partially and completely substituted examples. Tetramethyltetrazene-2,⁵⁰ $(CH_3)_2N-N=N-N-(CH_3)_2$, is a liquid distillable at $74^\circ/110$ mm.; 1,4-diphenyl-1,4-dimethyltetrazene-2 forms colorless leaflets, mp 137° dec., stable to boiling water, and tetraphenyltetrazene-2 forms yellowish crystals, mp 123° dec.⁵¹

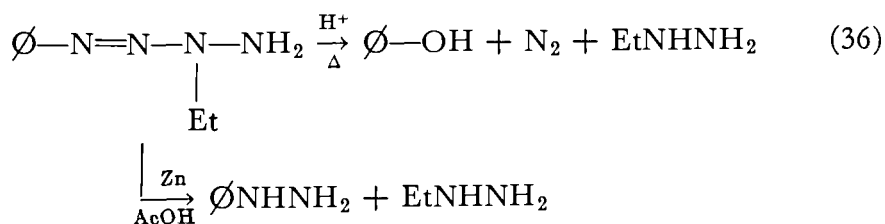
The 1-tetrazenes are prepared by the coupling of diazonium salts to hydrazines^{52, 53} (Eq. 34) (see Chapter 9). Support for the assignment



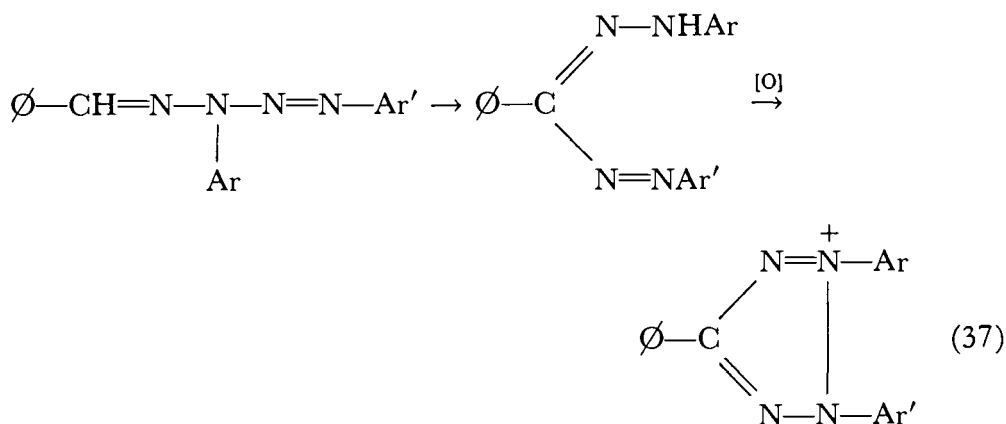
of the 1,3-disubstituted structure for the tetrazenes derived from monosubstituted hydrazines is adduced from the formation of hydrazones with aldehydes, identical to the products obtained by coupling diazonium salts to preformed hydrazones^{52a} (Eq. 35).



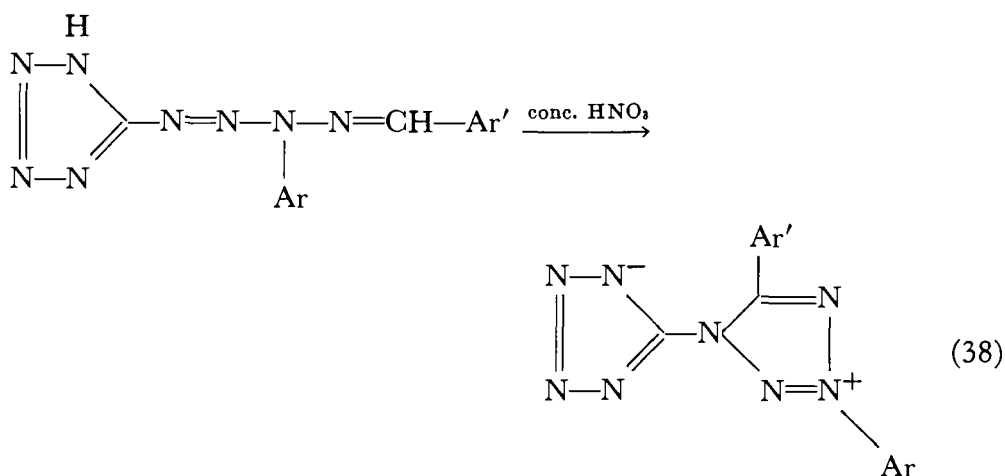
The 1-tetrazenes are presumably weakly basic and acidic, but they are decomposed by both alkalis and acids. The acid-induced decomposition evidently proceeds through initial decoupling; the products are a phenol, a hydrazine, and nitrogen.^{52b} Reduction gives a pair of hydrazines^{52b} (Eq. 36).



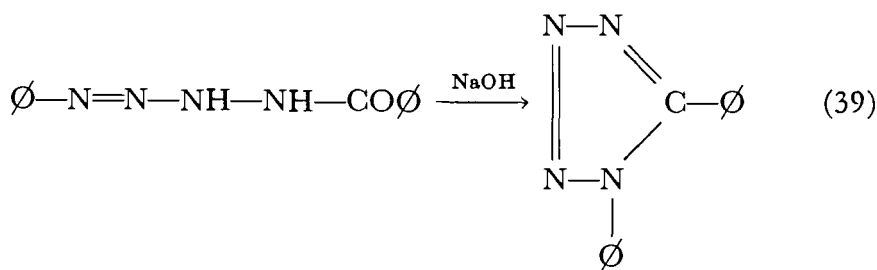
Alkylidene 1-tetrazenes undergo an interesting rearrangement to formazans on heating (Eq. 37); sodium ethoxide is a catalyst.^{54, 55} Oxida-



tion of benzyldene tetrazenes gives tetrazolium compounds, which may arise through formazans by the foregoing rearrangement, or, in the 1-tetrazolyl derivatives, may involve direct ring closure to give a 1,3,5- instead of a 2,3,5-trisubstituted tetrazolium system⁵³ (Eq. 38).

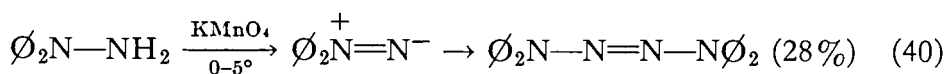


1-Aryl-4-acyl-1-tetrazenes are cyclized to tetrazoles by alkali⁵⁶ (Eq.

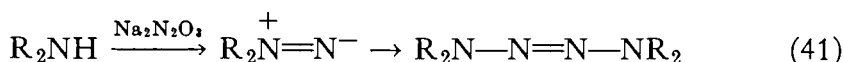


39). The 2-tetrazenes are formed from *unsym*-disubstituted hydrazines by oxidation in various ways,^{2, 50, 51, 57} including the decomposition of

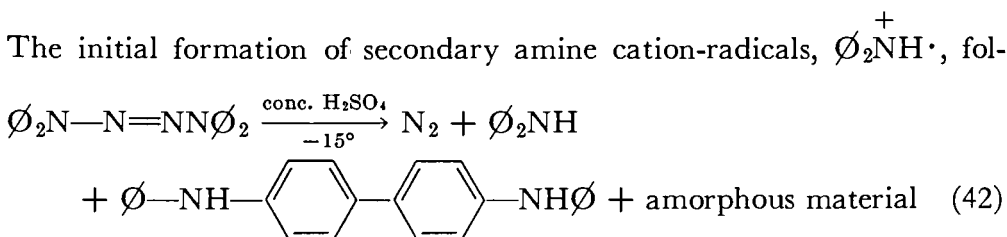
salts of the corresponding toluenesulfonyl derivatives; all these methods apparently gives rise to an intermediate azamine, $R_2N=N^+$, which dimerizes (Eq. 40) (see Chapter 9). They may also be generated from



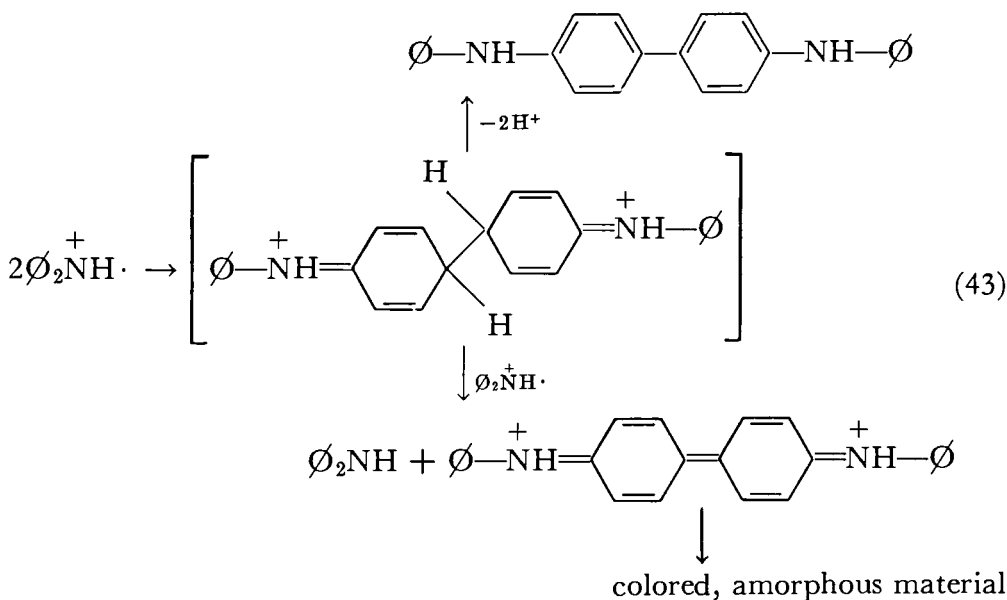
secondary amines by reaction with Angeli's salt ⁵⁸ (sodium nitrohydroxamate) (Eq. 41).

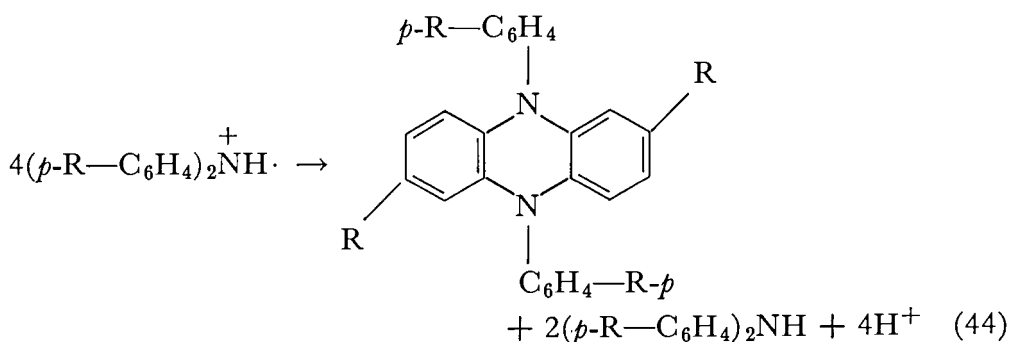


2-Tetrazenes are apparently weakly basic, but salts have not been isolated, for loss of nitrogen takes place as soon as 2-tetrazene solutions are acidified, and amines and other products are obtained ⁵¹ (Eq. 42).

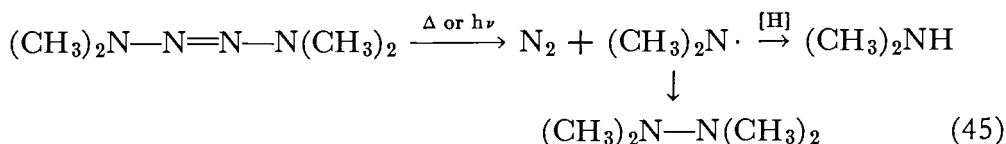


lowed by disproportionation, accounts for the observed products, which are benzidines or their oxidation products if *para* positions are open or 9,10-diarylphenazine derivatives ^{51, 57} (Eq. 43). When hydrochloric acid is used, the products may contain chlorine.



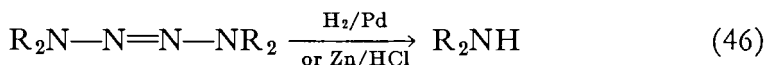


2-Tetrazenes are also decomposed by photolysis⁵⁹ and by mild heating (generally 80–120°),⁶⁰ which cause loss of the nitrogen and initial formation of secondary amino radicals (Eq. 45). The amino radicals then either dimerize to form hydrazines, or abstract hydrogen from the medium. A violet solid that appears to be composed of free dimethyl-



amino radicals has actually been isolated from the decomposition of tetramethyltetrazene followed by rapid quenching in liquid nitrogen⁶¹; at −160°, the color fades and tetramethylhydrazine and other products are formed. Decomposition of tetramethyltetrazene in the presence of olefins initiates polymerization.⁶⁰

Reduction of 2-tetrazenes catalytically or by dissolving metals always gives a secondary amine^{62, 63} (Eq. 46); neither tetrazanes nor hydrazines



have been reported. Stannous chloride, which will reduce azamines, the monomers corresponding to tetrazenes, does not reduce tetrazenes themselves.⁶⁴

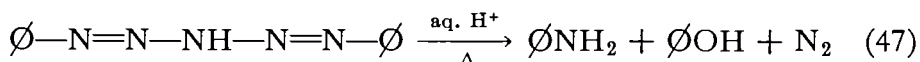
TETRAZADIENES

Whereas no simple tetrazadienes, $\text{R}-\text{N}=\text{N}-\text{N}=\text{N}-\text{R}$, have been reported, substances that can be considered as formally derived from such a structure are known in the form of N-azido amines, such as

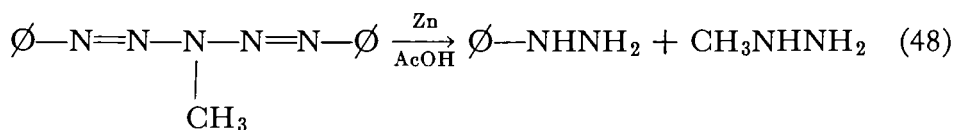
N-azido-*bis*-(trimethylsilyl)amine,⁶⁵ $[(\text{CH}_3)_3\text{Si}]_2\text{N}-\text{N}_3 \leftrightarrow [(\text{CH}_3)_3\text{Si}]_2\text{N}^+=\text{N}-\text{N}=\text{N}^-$, and N-azidodimethylamine,⁶⁶ $(\text{CH}_3)_2\text{N}-\text{N}_3$, bp 32°/11 mm.

PENTAZADIENES

Although no authentic pentazanes or pentazenes have been reported, 1,4-pentazadienes are known in considerable variety from the coupling of diazonium salts with primary amines,^{9, 67, 68} or with triazenes.⁶⁸ 1,5-Diphenylpentazadiene forms yellow prisms that explode on heating or rubbing.⁶⁸ It is acidic enough to dissolve in dilute alkali, but does not dissolve in cold, dilute acids. Hot acid brings about decomposition into aniline, nitrogen, and phenol (Eq. 47), presumably through initial decoupling to a diazonium salt and phenyltriazene. 1,5-Diphenyl-3-



methylpentazadiene forms bright yellow needles, mp 112–113°; cold acid breaks the compound into aniline, methylamine, nitrogen, and a diazonium salt.⁶⁹ Reduction gives both phenylhydrazine and methylhydrazine, and, presumably, aniline and methylamine (Eq. 48).



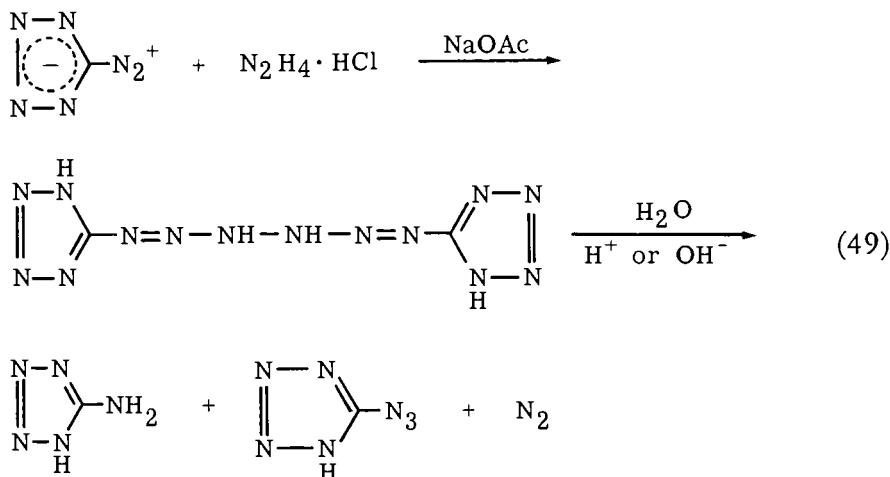
Although pentazadienes decompose on mild heating, often violently, little has been done to investigate the reaction. Free radicals are evidently formed, for pentazadienes have been used as polymerization initiators.⁷⁰

HEXAZADIENES

The only isolated example of a disubstituted hexazadiene appears to be the 1,6-*bis*-(5-tetrazolyl) derivative, a yellowish solid that is stable at room temperature but explodes at 90°, or when pressed.^{71, 72b} It is formed by the coupling of two moles of 5-diazotetrazole with hydrazine (Eq. 49), a reaction that has not been duplicated with benzenediazonium compounds apparently because the intermediate monosubstituted tetrazenes break up before they can be engaged by a second diazonium ion. This hexazadiene is acidic enough to form a sodium salt (yellow) with concentrated alkali, but it cannot of course be said with certainty whether the acidity is due to the hexazadiene hydrogens or the 1-tetrazolyl hydrogens.

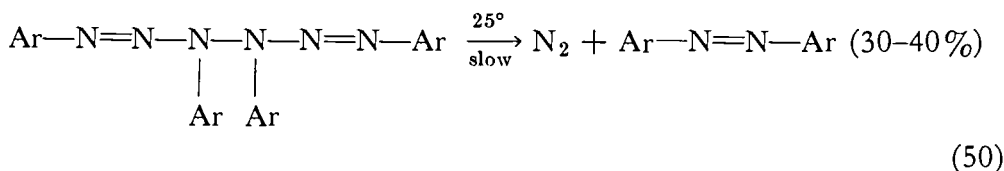
The hardly surprising, extreme sensitivity of ditetrazolylhexazadiene precluded analyzing it in the ordinary manner, but its constitution is

more or less adequately supported by a determination of its degradation products (Eq. 49).

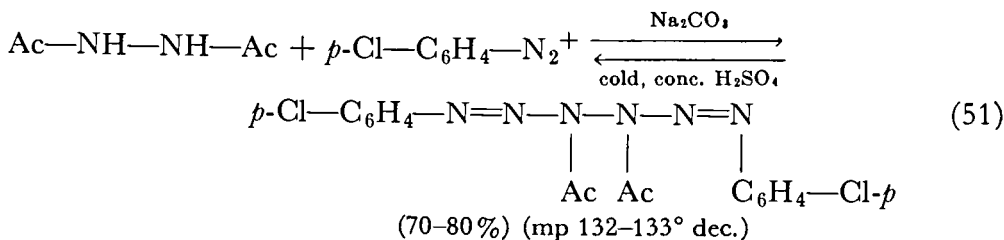


The simplest tetrasubstituted hexazadienes are 1,6-diaryl-3,4-dimethyl derivatives, obtained by the coupling of negatively substituted diazonium salts with *sym*-dimethylhydrazine ^{72b}; cold concentrated sulfuric acid reverses the coupling. 1,6-Bis-(*p*-chlorophenyl)-3,4-dimethyl-1,5-hexazadiene thus obtained is a slightly greenish solid, mp 86–87°; although it is stable to prolonged storage in a refrigerator and can apparently be handled “safely” when protected from shock, it explodes when heated or struck.

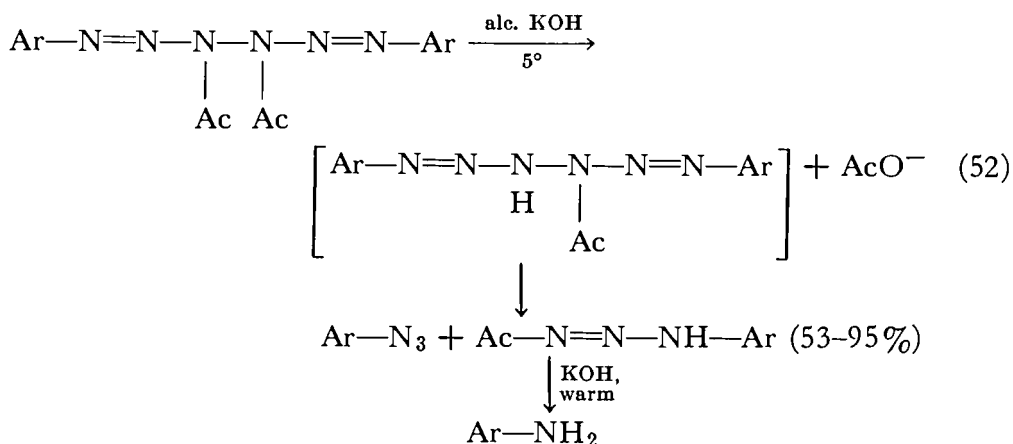
A group of tetraarylhexazadienes has been prepared by the oxidation of diaryltriazenes.³³ They are not very stable, and only those bearing electron-withdrawing substituents have been isolated. 1,3,4,6-Tetrakis-(*p*-chlorophenyl)hexazadiene is a yellow solid that decomposes at 110°; even at room temperature, slow decomposition to nitrogen and an azobenzene is noticeable (Eq. 50).



Although the coupling of diazonium salts to hydrazine is not a generally successful route to hexazadienes, secondary hydrazides give 3,4-diacyl hexazadienes more readily ⁷² (Eq. 51). They are colorless, crystal-



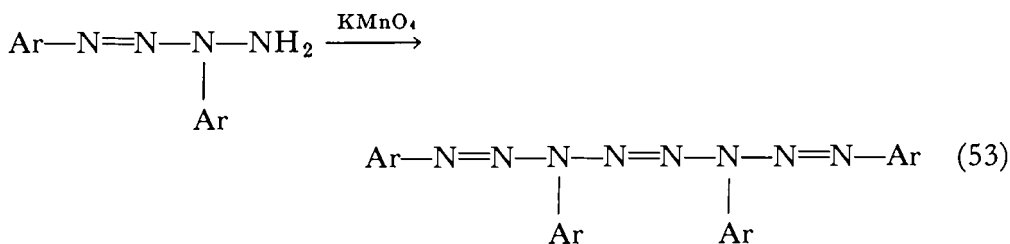
line solids whose ultraviolet spectra have a strong maximum near 290 $m\mu$; they melt with decomposition at temperatures well above 100°. Alcoholic potassium hydroxide first cleaves the diacyl hexazadienes into a mole each of aryl azide, aryl acyl triazene, and nitrogen, the expected decomposition products of the presumed intermediate monoacyl hexazadiene (Eq. 52). Hot hydrochloric acid is almost without action on the



diacyl hexazadienes, but cold, concentrated sulfuric acid effects decoupling in a few minutes, regenerating the diazonium salt and hydrazide from which the compound was prepared.

OCTAZATRIENES

A small group of 1,3,6,8-tetraaryloctazatrienes has been reported as products in low yield of the oxidation of 1,3-diaryltetrazenes³ (Eq. 53). The tetraphenyl derivative, for which no analysis was reported, is an explosive, difficultly soluble, sulfur-yellow solid, mp 51–52°. The 3,6-diphenyl-1,8-*bis*-(*p*-tolyl) analog was analyzed, but there was a discrepancy



of 0.5% in the carbon analysis, and more in hydrogen; the nitrogen analyses of the 3,6-diphenyl-1,8-*bis*-(*p*-bromophenyl) and 1,3,6,8-tetrakis-(*p*-bromo-phenyl) analogs, were good, however. These substances have been claimed to be initiators for radical-induced polymerization.⁷⁰

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chapter
thirteen

C-Nitroso Compounds

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NOMENCLATURE

Nitroso compounds are named solely by use of the prefix “nitroso” with a suitable locant, as in “2-nitrosopropane.” The dimers of nitroso compounds have usually been named by use of the prefix *bis*, as in “*bis*-(nitrosomethane)” a system that had the advantage of implying nothing about the structure of the dimers at a time when their structure was uncertain. Now that linkage through the nitrogen atoms has been established, it may occasionally be desirable to name the dimers as N,N'-dioxides of azo compounds or as diimide N,N'-dioxides (cf. the following section). In the older literature, the stable dimers were named “*bis*-nitrosylalkyls” and are listed in Beilstein under hydroxylamines in the main work.

The term “pernitroso” has been used in the past for a divalent group N_2O_2 , but it is now believed that the compounds concerned are actually nitrimines, $\text{O}_2\text{N}-\text{N}=\text{CR}_2$ (cf. Chapter 15). “Isonitroso” is an obsolete term for the hydroximino group of oximes, which are isomeric with nitrosoalkanes.

gem-Nitroso-nitro compounds, $\text{ON}-\text{CR}_2-\text{NO}_2$, are given the class name “pseudonitrole.” 1-Nitrosoaldoximes, $\text{HON}=\text{CR}-\text{NO}$, whose

anions form a symmetrically delocalized system, $\text{RC}(\text{NO})_2^-$, are called nitrosolic acids, such as acetone nitrosolic acid, $\text{CH}_3-\text{C}(\text{NO})=\text{NOH}$. In the older literature this compound is given the misleading name "ethyl-nitrosolic acid." The collective term nitrosites is commonly applied to β -nitro nitroso compounds, obtained from the addition of nitrogen trioxide to olefins.

PROPERTIES ¹

Nitroso compounds are intense blue or green substances that equilibrate to variable extents with colorless dimers. Most examples exist as the dimers in the solid state, but dissociate on melting or vaporization; for this reason, the apparent melting points are intimately bound up with the dissociation phenomenon. Dissociation may also take place on solution, as shown by the development of color. In several instances, two forms of the dimer are known; these owe their existence to geometrical isomerism, as will be discussed presently.

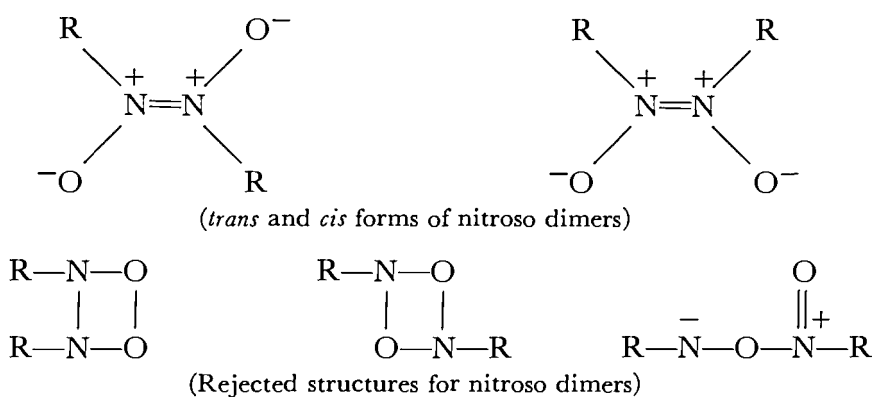
trans-Bis(nitrosomethane) melts at 122° and is soluble in water, alcohol, or acetone, difficultly soluble in ether or carbon tetrachloride, and insoluble in pentane. The *cis* isomer melts at $93.5\text{--}95^\circ$. *trans-Bis*(*tert*-nitrosobutane), (*t*-Bu-NO)₂, melts at $83\text{--}84^\circ$ followed rapidly by vaporization (monomer). Nitrosobenzene exists as a pale greenish solid, mp 68° , and forms an emerald green melt that boils at $57\text{--}59^\circ/18\text{ mm}$. Trichloronitrosomethane, which is a monomer, boils at $57\text{--}58^\circ$ with decomposition.

The blue color of monomeric nitroso compounds is due to an $n \rightarrow \pi^*$ transition that absorbs weakly in the $6300\text{--}7900\text{ \AA}$ range ($\epsilon = 1$ to 60); additional bands at $2700\text{--}2900\text{ \AA}$ ($\epsilon = 80$) and $2200\text{ \AA}$ ($\epsilon = 5000$) also appear. The stretching frequency in the infrared of the NO bond has been observed between 1539 and 1621 cm^{-1} . Nitroso *trans*-dimers absorb moderately strongly ($\epsilon \sim 9000$) near $2950\text{ \AA}$; the *cis* isomers absorb at shorter wavelengths (e.g., *cis-bis*(nitrosomethane) $2640\text{ \AA}$).² The *trans* dimers show a strong band in the infrared ^{1, 3-5} at $1176\text{--}1299\text{ cm}^{-1}$, attributed to NO stretching; in the *cis* isomers, this band is replaced by a doublet at higher frequencies ($1323\text{--}1344$ and $1330\text{--}1420\text{ cm}^{-1}$ for aliphatic, $1389\text{--}1397$ and 1409 cm^{-1} for aromatic).

Crystalline *p*-iodonitrosobenzene, which is a green monomer, has been examined by X-ray crystallography⁶; it has the bond distances C—N = $1.28\text{ \AA}$ and N—O = $1.24\text{ \AA}$, and the C—N—O angle is 125° . The C—N distance is much shorter than that observed in aliphatic amines ($1.49\text{ \AA}$) and suggests a considerable degree of overlap between the

π -orbital of the NO system and that of the benzene ring; the geometry corresponds to sp^2 hybridization about the nitrogen.

The easy monomer-dimer equilibrium and uncertainties about the structure of the dimers have complicated the interpretation of nitroso chemistry for a very long time. The difficulties are further compounded by the lability of the nitrosoparaffin monomers toward isomerization to oximes (discussed under Reactions). Only in recent years has sufficient evidence been assembled to render indisputable the structure formally corresponding to an N,N' -dioxide of an azo compound; the manner of bonding, however, remains an object of discussion. The evidence for the structure should be considered in comparison to the alternate structures: 1,2,3,4- or 1,3,2,4-dioxadiazetidines, or an open-chain, unsymmetrical dipolar structure.



Chemical evidence consists of the absence of reactions typical of peroxides, the existence of pairs of isomers, and the reduction of certain very stable dimers to disubstituted hydrazines.⁷ Such evidence by itself is obviously less than conclusive, for the dioxadiazetidines might account for the observed isomers, and the 1,2,3,4-dioxadiazetidine could easily give rise to a hydrazine on reduction. A further piece of chemical evidence, the fact that nitrosobenzene undergoes electrophilic substitution in the *ortho* and *para* positions, seemed to favor the dioxadiazetidine structures, for the monomer and the azobenzene- N,N' -dioxide structure would be expected to exhibit *meta* orientation. This evidence was later vitiated when it was discovered that electrophilic substitution actually takes place through addition compounds of the nitroso group with such substances as hydrogen bromide, rather than by direct substitution on the nitroso compound or its dimer.⁸

The question was ultimately settled by means of physical evidence. Reported dipole moment data have been judged to be inconclusive, because of unjustified assumptions made in their calculation^{1, 9}; the

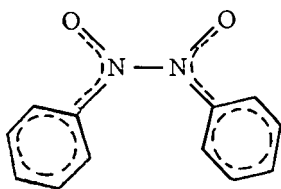
dipole moment of *trans-bis*(nitrosomethane) actually appears to be very small, if not zero. The infrared spectra, however, are compatible only with structures having bonds stronger than the N—O single bond. X-Ray crystal-structure determinations have been made on several nitroso dimers, including the intramolecular *cis* dimer of 1,4-dichloro-1,4-dinitrosocyclohexane,¹ *trans-bis*(*p*-bromonitrosobenzene),^{1, 10} and *trans-bis*(1-nitrosoisobutane).¹¹ The short bond distances (N—N, 1.27 to 1.31 Å; N—O, 1.30 to 1.35 Å) as well as the atomic positions indicate a gross structure of the diimide N,N'-dioxide type with bond orders greater than 1. The ONNO system is planar or nearly so, and in 1-nitrosoisobutane dimer, the angles about the nitrogen are close to 120°. Finally, the nuclear magnetic resonance spectra of nitrosoalkane dimers, such as *trans-bis*(α -nitrosotoluene) show a symmetrical structure with identical α -hydrogens, whose chemical shift is similar to those of azoxy compounds for the hydrogens adjacent to the oxygenated nitrogen.¹²

The stability of nitroso dimers with respect to the monomers is considerably influenced by structure. The nitrosoparaffin dimers are thermodynamically much more stable than the monomers¹³ (in the order of 25 kcal/mole) if electron-withdrawing groups are absent, and although the dimers can usually be cleaved by moderate heating, the process may be slow. Accumulation of electron-withdrawing substituents stabilizes the monomers. The stable configuration of the nitrosoalkane dimers has been recognized¹⁴ as *trans* by comparing their spectra to those of cyclic internal dimers, such as 1,4-dichloro-1,4-dinitrosocyclohexane and 2,2'-dinitrosobiphenyl, whose structure enforces a *cis* configuration. The more energy-rich *cis* isomers are sometimes the initial products of reaction, however.

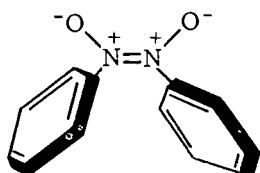
In contrast to aliphatic nitroso compounds, nitrosobenzene derivatives are generally more stable thermodynamically as monomers in solution, and electron-donating substituents (in the *para* position) enhance the stability of the monomers. *Ortho* substituents of any kind, however, markedly enhance the relative stability of the dimers. *p*-Dimethylaminonitrosobenzene and *p*-iodonitrosobenzene, for example, are green monomers even in the crystalline state, whereas *o*-iodonitrosobenzene is a colorless dimer. The geometrical configuration of the dimers, as revealed by spectrographic data, is *cis* for nitrosobenzene and α -nitrosonaphthalene, whereas in certain other examples it is *trans*; apparently no single aromatic nitroso dimer has yet been obtained in both *cis* and *trans* configurations.

The foregoing facts have been correlated by the assumption that the dimeric structure is inherently more stable, but conjugation with substituents shifts the relative stability toward the monomer.^{1, 13} Conjugation in nitrosobenzene dimers would be less effective in the *cis* configuration, owing to steric interference between *ortho* hydrogens when the rings

are fully coplanar with the ONNO system, the conformation enabling maximum π -orbital overlap. The phenyl groups must be twisted out of



(coplanar *cis* configuration;
full conjugation)

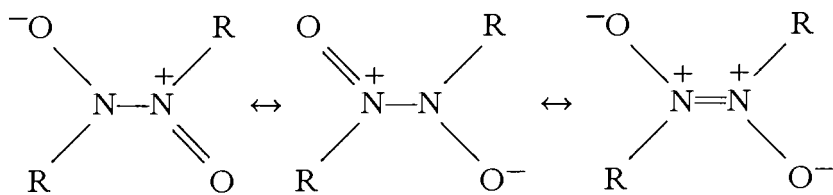


(twisted *cis* configuration;
repressed conjugation)

the plane to avoid interference. Such twisting represses conjugation between the ONNO system and the ring, which otherwise competes with the conjugation within the ONNO system; the N—N bond, which holds the dimer together, would be more nearly a double bond and therefore stronger, in the absence of conjugation with the ring. *Ortho* substituents would clearly enhance this effect, for interference between the *ortho* substituents and the oxygen atoms of the ONNO system would occur even in the *trans* configuration when the system is coplanar. Electron-donating *para* substituents have the reverse effect, as would be anticipated, owing to enhancement of conjugation with the ring. The x-ray structure determination of *p*-bromonitrosobenzene, which exists as the *trans* dimer in the crystalline state, reveals that here, too, the benzene rings are twisted out of the ONNO plane.¹⁰

An alternative explanation,^{13c} in terms of steric inhibition of conjugation in the *monomer*, has been offered for the stabilizing effect of *ortho* substituents on nitrosobenzene dimers. This implies a higher energy content in *ortho*-substituted nitroso monomers, which is supported by their greater ease of polarographic reduction. This explanation, which is otherwise very attractive, does not so readily account for the stability of *cis*-nitrosobenzene dimer over the *trans* isomer.

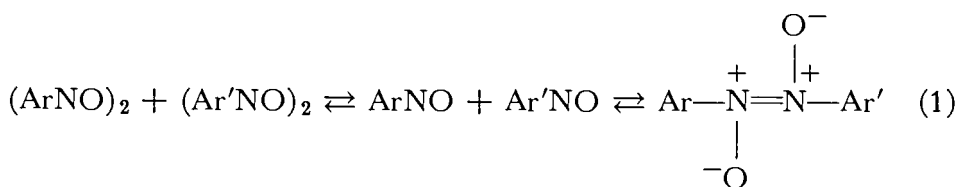
The foregoing discussion implies that the stability of nitroso dimers may be bound up with conjugation in the ONNO system, which would be weakened by cross conjugation with substituents. In fact, structures representing such conjugation were proposed some time ago to account for the properties of the dimers.¹⁵ An electronic arrangement with bonds of order $\frac{3}{2}$ has more recently been proposed.¹⁶



(Hammick formulation of nitroso dimers)

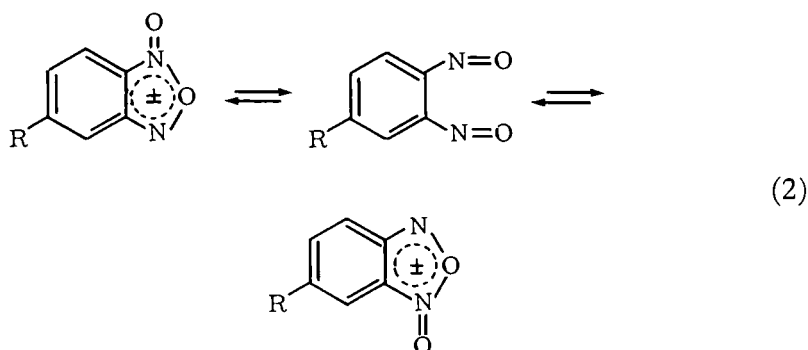
The dimerization process goes readily in nonpolar solvents.¹⁷ The kinetics of cleavage of dimers to monomers are unimolecular, but are complicated by strong solvent effects, which alter both the enthalpy and the entropy of activation.^{18, 19} Water, for example, markedly retards cleavage.¹⁴ Solvent effects are also strong in the isomerism of *cis* to *trans* dimers, which takes place most readily in nonpolar solvents; the reverse change may sometimes be accomplished by irradiation.¹⁴ The mechanism of geometrical inversion has not been established, but the similarity of the solvent effects with those on the monomer-dimer interconversion suggests that cleavage and recombination is a significant path. This is consistent with the fact that isomerization of primary and secondary nitrosoalkanes in the undiluted melt, in which the monomer concentration would be highest, takes place with much less competition from the prototropic rearrangement to oximes than in solution,¹⁴ where the second-order recombination of monomer would be retarded with respect to a first-order prototropic rearrangement. *Trans* dimers are markedly more volatile than the *cis*,^{19c} sufficiently so as to allow separation by fractional sublimation. Since the *trans* isomers are ordinarily the more stable, the difference in volatility cannot be due to the difference in ease of dissociation, and it has thus at least been established that the dimeric molecules are capable of existence in the vapor phase.

Unsymmetrical dimers derived from two different nitroso monomers should in principle be capable of existence. With aromatic nitroso compounds, equilibration is apparently too fast to permit isolation ^{20a} (Eq. 1), but a mixed nitrosoheptane-4-nitroso-1-octanol dimer has been isolated as an oil that slowly equilibrates with the symmetrical dimers.^{20b}



The dimers of *o*-dinitrosobenzenes deserve special mention. Compounds formally corresponding to *o*-dinitrosobenzenes or their intramolecular "dimeric" equivalent can be obtained easily by straightforward reactions. They are colorless to yellow and in that respect differ markedly from nitroso monomers; they have usually been considered as benzofuroxans. The consistent failure of numerous attempts to obtain isomeric 3- and 6-substituted benzofuroxans is not consistent with a fixed benzofuroxan structure, however. Two explanations have been offered ²¹: the supposed benzofuroxans are actually *o*-dinitrosobenzenes in which the properties of the nitroso groups are markedly altered by electronic inter-

action, or 3- and 6-substituted benzofuroxans can equilibrate with each other unusually easily, presumably through the intermediacy of the dinitroso structure (Eq. 2). The nuclear magnetic resonance spectrum



of benzofuroxan below room temperature does not show the A_2B_2 pattern to be expected of the symmetrical dinitroso structure, but the patterns appears at higher temperatures; this is taken to favor the equilibration alternative.²²

Neither nitroso compounds nor their dimers show basic properties in the presence of water, but adducts with some strong acids, such as hydrogen chloride, have been obtained in nonaqueous medium,^{8, 23} and a value of $pK_a \simeq 0$ has been determined for nitrosobenzene in absolute methanol.²⁴ Nitroso compounds having α -hydrogens would be expected to have a feeble acidity, in analogy with nitro compounds. The resulting anion, $R_2\bar{C}-NO$, would be indistinguishable from that of the corresponding oxime, $R_2C=NO^-$, and bases do, in fact, accelerate the rearrangement to oximes.¹⁷

The characteristics of the nitroso group as an electron-withdrawing aromatic substituent capable of engaging in conjugation with electron pair donors is revealed by dipole moments¹ as well as by chemical behavior. Whereas nitrosobenzene has a moment of 3.2 D, in *p*-nitronitrosobenzene (monomer) the moment is only 0.84; in *p*-dimethylaminonitrosobenzene, the moment, 6.90 D, considerably exceeds the vector sum (4.81 D) of the moments of dimethylaniline and nitrosobenzene.

REACTIONS

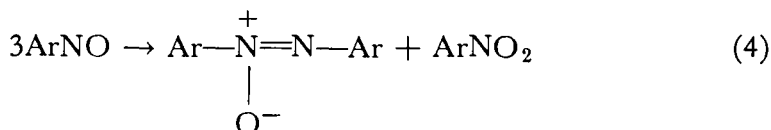
Usually it is difficult to tell whether an observed reaction should be attributed to a nitroso monomer or to its dimer, owing to facile interconversion. For this reason, the reactions of both monomers and dimers are treated together here, and a distinction is made only where the situation clearly allows.

ISOMERISM WITH OXIMES Prototropic rearrangement to oximes (Eq. 3) is the dominant reaction of primary and secondary nitrosoalkanes. This

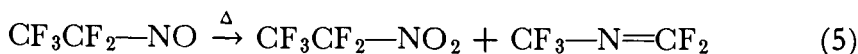


reaction occurs in the gas phase, in a melt, or in solution, often quite rapidly, and is not detectably reversible. Nitrosomethane, for example, undergoes rearrangement faster than dimerization at room temperature.¹⁴ The vapor-phase kinetics of isomerization of nitrosomethane are first order, but a surface reaction contributes significantly to the process.²⁵ The highly negative entropy of activation is consistent with an intramolecular, quasi-cyclic hydrogen transfer. Many substances accelerate the reaction, particularly polar and hydroxylic solvents,^{17a, 18} strong acids, bases,^{17a, 26} and nitric oxide.²⁵ It is not fully established that nitroso dimers can isomerize to oximes without first dissociating into monomer, but there are indications that certain acid- and base-catalyzed reactions may take place through direct conversion; *bis*(nitrosocyclohexane), for example, is converted to cyclohexanone oxime hydrochloride in 88% yield on standing at room temperature for two days in a cyclohexane solution saturated with hydrogen chloride.^{27a} However, the kinetics of the rearrangement of secondary nitroso compounds catalyzed by hydrogen chloride are first order, dependent on dimer concentration only; this strongly suggests that the rate-determining step is dissociation into monomer.^{27b}

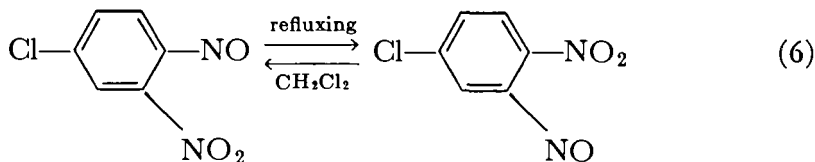
HEAT Heating nitroso compounds that cannot undergo a prototropic shift allows alternative reactions to come to light. Disproportionation into a nitro and an azoxy compound (Eq. 4) is typical of nitrosobenzenes.²⁸



Fully halogenated nitrosoalkanes also yield the corresponding nitro compound on heating, together with various other products, whose nature depends on structure and conditions.^{29, 30} Photolysis gives similar results. These reactions are best explained by supposing that the first step is cleavage of the C—N bond to give nitric oxide and a free radical; action of the nitric oxide on more nitroso compound could give rise to the observed nitro compounds, as is discussed further on. Perfluoronitrosoethane undergoes skeletal rearrangement in addition to giving nitro compound³¹ (Eq. 5).

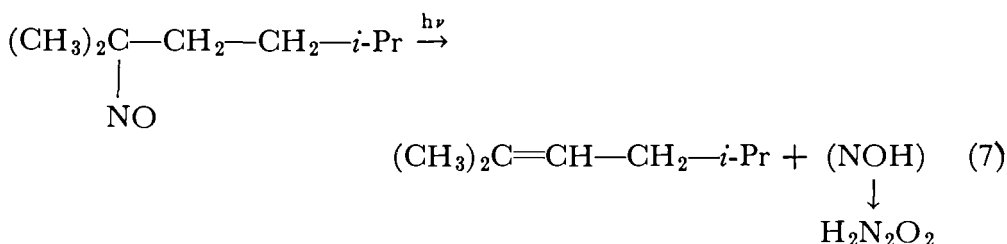


A thermal reaction of another type has been observed with vicinal nitro nitroso benzenes. Oxygen transfer takes place, perhaps through an intermediate furoxan N-oxide, to give an equilibrium mixture of isomers ³² (Eq. 6). This reaction is closely related to the nitrosite re-

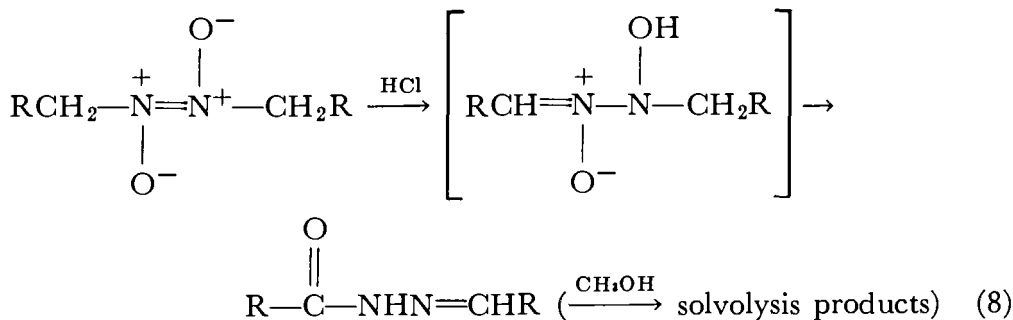


arrangement, discussed further on.

PHOTOLYSIS Two instances have been reported of the photolysis of aliphatic nitroso compounds; nitroxyl (isolated as silver hyponitrite) was eliminated and an ethylenic double bond formed ³³ (Eq. 7). The quantum yield was 1.

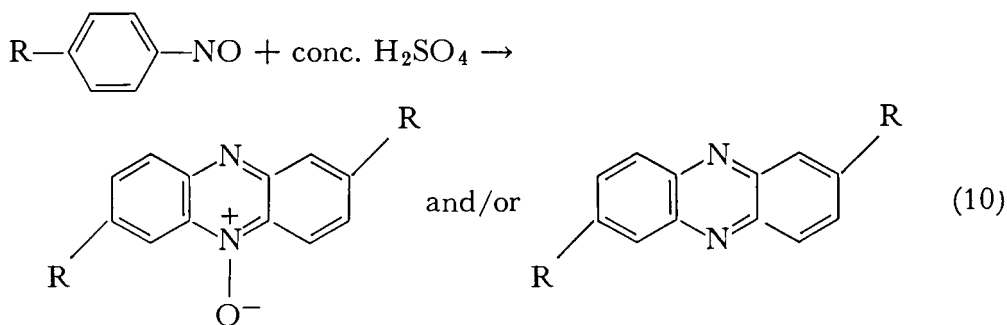
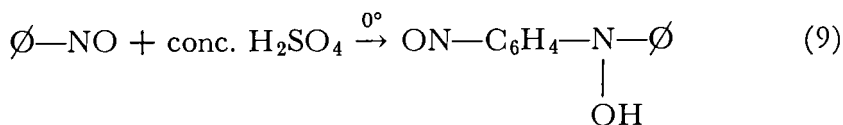


ACIDS Although nitroso compounds and their dimers show no basic reaction toward aqueous acids, adducts with the hydrogen halides have been detected and in at least one case isolated: *trans*-bis(nitrosomethane) forms a white solid of composition $\text{CH}_3\text{NO}\cdot\text{HCl}$ when treated with dry hydrogen chloride.²³ *Bis*(α -nitrosotoluene) reacts exothermically with hydrogen chloride in chloroform, forming principally benzhydrazide and benzyl chloride, accompanied by small amounts of several other substances,^{34, 35} such as benzylidenebenzhydrazide and N',N' -dibenzylbenzhydrazide; alkylidene hydrazides are apparently the primary products ^{27b} (Eq. 8). This type of product is clearly derived from the undissociated



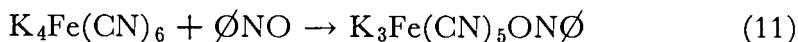
dimer, and its formation is analogous to the reactions of aliphatic azoxy compounds with acid. This type of reaction is observed only with dimers of primary nitroso compounds; the kinetics are first order each in dimer and hydrogen chloride.

Aromatic nitroso compounds, which can take part in neither of the foregoing reactions, undergo condensations when treated with concentrated strong acids. If the *para* position is free, nitrosodiarylhydroxylamines are formed (Eq. 9); otherwise, phenazines (Eq. 10), and/or their



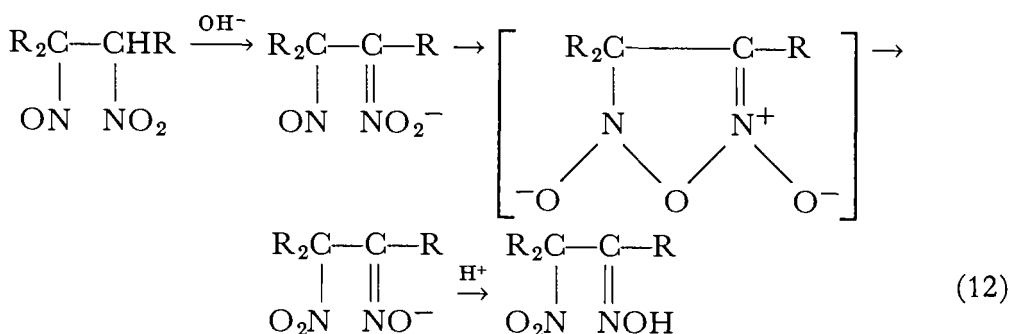
N-oxides, plus small amounts of N,N-diarylhydroxylamines may be formed.³⁶⁻³⁸

COMPLEX FORMATION Although the nitroso group is not very basic, nitroso compounds can become ligands in some complexes of transition metals. Potassium ferrocyanide, for example, reacts with nitrosobenzene with displacement of a cyanide ion^{39a} (Eq. 11). It seems not unlikely

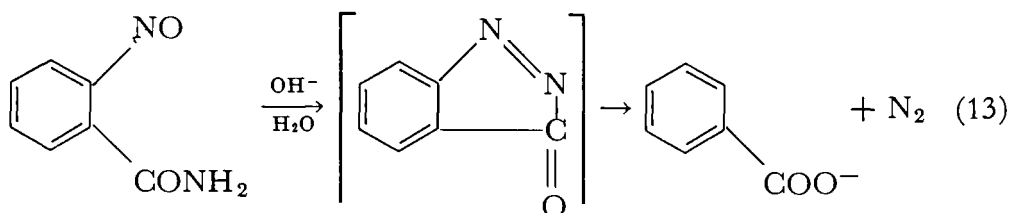


that this reaction is analogous to the formation of nitroprusside ion, and that the nitroso compound is not bound simply as a Lewis base. The formation of such complexes from pentacyanoammine ferroates is particularly easy, and since the products are intensely colored, their formation can be adapted to the qualitative detection of nitroso compounds.^{39b}

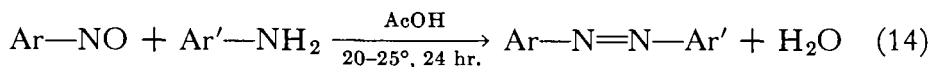
BASES Nitroso compounds are ordinarily inert to alkalis, except for catalysis of the rearrangement of nitrosoalkanes to oximes. Nitrosites— β -nitronitrosoalkanes—present a special case, however. Those in which the nitroso group is on a tertiary carbon, and thus as such incapable of isomerization to oximes, undergo transfer of an oxygen atom from the adjacent nitro group, which, now become a nitroso group, isomerizes to an oxime⁴⁰ (Eq. 12). Another case of base-catalyzed interaction with



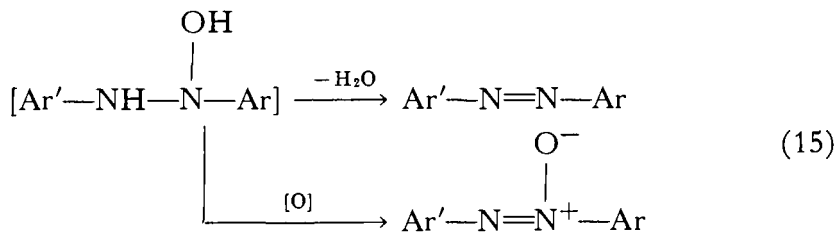
a vicinal function is the denitrosation of *o*-nitrosobenzamide ⁴¹ (Eq. 13).



AMINES Primary aromatic amines condense with aromatic nitroso compounds to form azo compounds (Mills reaction)^{42–44} (Eq. 14); the



reaction is fairly general. The components usually react satisfactorily in glacial acetic acid on standing for a day, but certain pyridylamines that are unreactive under these conditions have been induced to react by forming their sodium derivatives with sodamide.⁴⁴ Reaction presumably passes through the stage of a hydroxyhydrazine. Although such substances have never been identified, evidence for their existence can be seen in the occasional appearance of azoxy compounds as by-products, which presumably arise when oxidation (probably by excess nitroso compound) is fast enough to compete with dehydration ⁴⁵ (Eq. 15). The condensation of substituted nitrosobenzenes with anilines is one of the



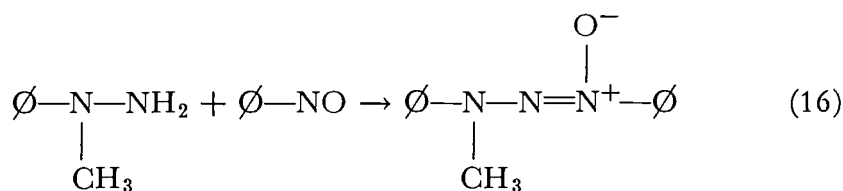
many reactions whose kinetics reveal a linear relation between the energy and entropy of activation.⁴⁶

Reports of reactions of nitroso compounds with aliphatic amines are scanty, and since piperidine has been used successfully as a catalyst for

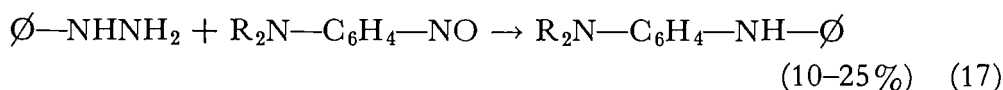
other reactions of nitroso compounds, reactions with such amines apparently do not occur readily. Indeed, some nitrosopyrimidines have been shown to undergo reaction with amines at other sites in the molecule without involving the nitroso group.⁴⁷ On the other hand, an instance of an oxidation-reduction reaction between nitrosobenzene and a secondary amine, leading to azobenzene and N,N-dialkylhydroxylamine, has been reported.⁴⁸

With diarylamines, such as diphenylamine or N,N'-diphenylbenzidine, condensation at a *para* position occurs when concentrated sulfuric acid is used as a catalyst, giving intensely blue quinonimine derivatives, whose formation has been adapted as a test for nitroso compounds on a micro scale.⁴⁹

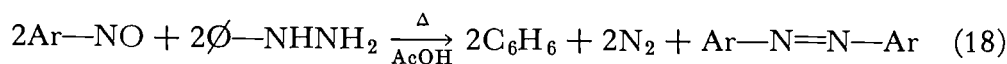
The condensation of nitrosobenzenes with *unsym*-disubstituted hydrazines is on the whole similar to that with anilines, with the difference that oxidation of the presumed N-hydroxy intermediate predominates overwhelmingly over dehydration⁵⁰ (Eq. 16). The literature about the



reaction of phenylhydrazine with nitrosobenzenes is in part conflicting. In some cases, the corresponding diarylamine is a significant product (Eq. 17); isotope-labeling experiments have shown that the amino nitro-



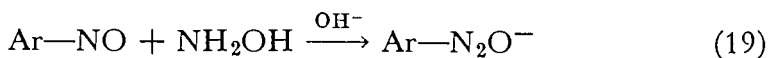
gen comes almost solely from the nitroso group, which implies that the amine did not arise by decomposition of a triazene first formed.⁵¹ Azobenzene has been reported as the sole product when phenylhydrazine is added slowly to a large excess of nitrosobenzene in unheated acetic acid.^{42a} N-Hydroxydiaryltriazenes have been reported to be the major products, according to an apparently extensive investigation, the experimental details of which have never been published.⁵⁰ In contrast to both of these claims, a quantitative gasometric analytical method for C-nitroso compounds has been developed^{42b} according to Equation 18, which is



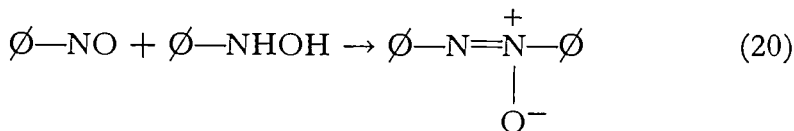
obeyed when a nitroso compound is warmed with an excess of phenylhydrazine in acetic acid, it is claimed.

Nitrosobenzenes condense with hydroxylamine in the presence of alkali to give *syn*-diazotates⁵² (Eq. 19). N-Aryl and N-alkyl hydroxyl-

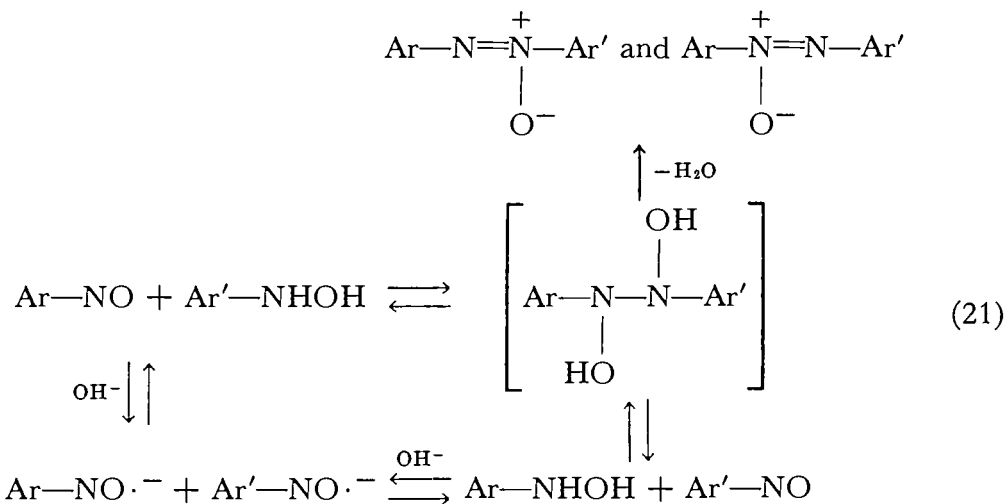
amines condense easily with nitrosobenzenes (and even with nitrosoalkane



dimers ^{53a}), producing azoxy compounds (Eq. 20) (cf. Chapters 8, and

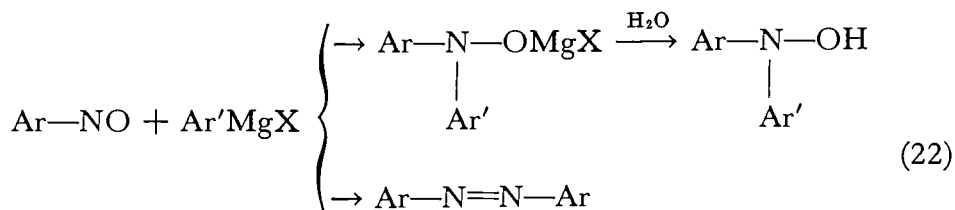


11: "Preparative Methods"). When the nitroso compound has a group different from the group on the hydroxylamine, not only may both possible asymmetrical azoxy compounds be formed, but symmetrical ones as well. ^{24, 53b} This indicates that there is rapid redox equilibration between the reactants, perhaps taking place through an intermediate N,N'-dihydroxyhydrazine (Eq. 21). In support of this view is the observation ^{53c}



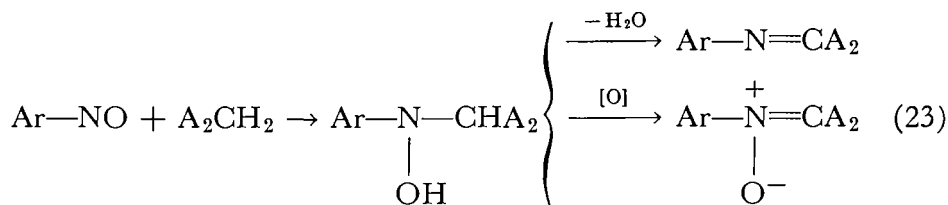
that only one-half of the isotope is lost (as water) when one of the reactants is labeled with O¹⁸. In alkaline solution, however, equilibration through anion radicals is demonstrable. ⁵⁴

GRIGNARD REAGENTS Nucleophilic carbon species of various types react with nitroso compounds; the common first step is attachment of carbon to the nitroso nitrogen. With Grignard reagents, the reaction commonly goes no further, and N,N-diarylhydroxylamines can be prepared readily ^{55, 56} (Eq. 22). When there are electron-donating groups



on the nitrosobenzene, however, addition does not occur, and only reduction to an azobenzene is observed.⁵⁴ The addition reaction is not a vigorous one, but is preceded by exothermic formation of isolable adducts, from which the nitroso compound is regenerated on hydrolysis⁵⁷; formation of a hydroxylamine requires a considerable excess of Grignard reagent,^{55b} which may unavoidably have the undesired effect of reducing some of the magnesium derivative of the diarylhydroxylamine to diarylamine.⁵⁶ The possibility may reasonably be entertained that nitroso anion radicals are involved in these transformations.⁵⁴

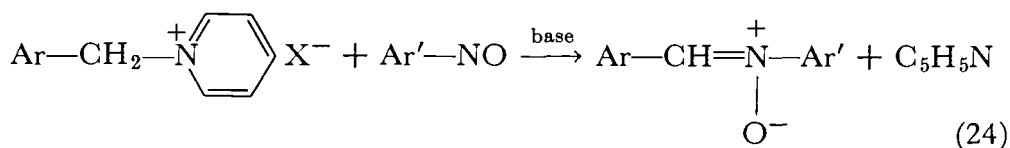
ACTIVE METHYLENES Active methylene compounds in general react with nitroso compounds in the presence of a basic catalyst, such as pyridine or sodium carbonate; the products are either anils,⁵⁸ resulting from loss of water from the primary adduct (Ehrlich-Sachs reaction), or nitrones,^{55a} resulting from oxidation of the primary adduct (Eq. 23). Interpretation



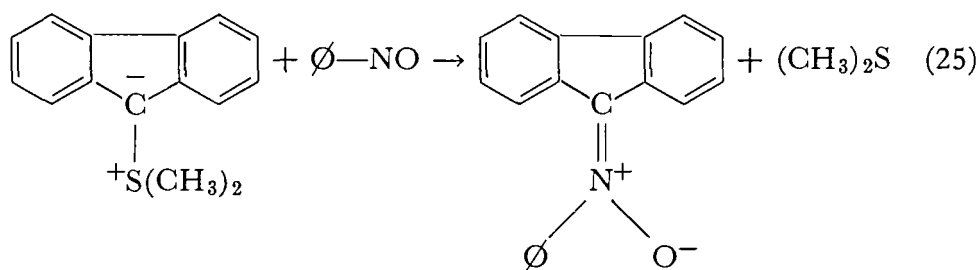
of the factors that determine which type of reaction will predominate on the basis of the sporadic investigations reported is not very satisfactory. The situation is beclouded, especially in the earlier reports, by the failure to report yields or to obtain even an approximate material balance, failure to control atmospheric oxidation as a possible experimental variable, and failure to recognize the occurrence of secondary transformations of the anils and nitrones. The reaction of *p*-dimethylaminonitrosobenzene with arylacetonitriles has been observed to give predominantly nitrone when catalyzed by weak bases at lower temperatures, whereas hot alkali favors anil formation.⁶⁰ On the other hand, the condensation of 2,4-dinitrotoluene with *o*-nitrosotoluene shows the reverse effect, piperidine favoring anil formation, sodium carbonate favoring nitrone (isolated as a transformation product, 2,4-dinitrobenzo-*o*-toluidide).⁶¹ The formation of benzanilides by the subsequent isomerization of the nitrones produced by the reaction of activated toluenes with nitrosobenzenes is a common occurrence (cf. Chapter 8). The effect of this and other base-catalyzed transformations of nitrones has been demonstrated by a study of yields as a function of reaction time; the yields of anil remain approximately constant, but the yields of nitrone rapidly fall to nearly zero.⁶² The rough generalization emerges from the scattered literature that aliphatic active methylene compounds tend to produce anils predominantly, whereas activated toluenes (such as TNT) are more prone to give nitrone, but the basis is not a strong one. Anil formation

from compounds activated by cyano groups, such as cyanoacetic ester, may be severely complicated by subsequent condensations and reactions involving the cyano group.⁵⁸

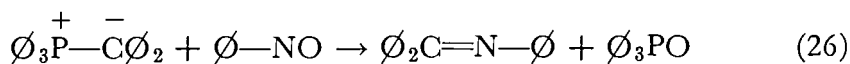
A variant of the foregoing reaction, the use of N-benzylpyridinium salts as the potential carbanions, gives rise exclusively to nitrones (Eq. 24); it is known as the Kroehnke reaction.^{59, 63} In this reaction, ob-



viously, no oxidation step is needed to give rise to nitron. A similar reaction occurs between nitroso compounds and quaternary Mannich bases.⁶⁴ Both of these reactions probably proceed through formation of ylides. Indeed, the reaction of preformed sulfonium ylides with nitrosobenzenes to give nitrones appears to be a general reaction⁶⁵ (Eq. 25).

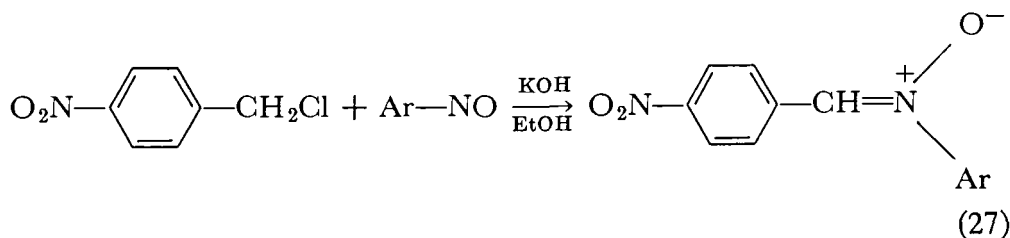


Phosphonium ylides, however, give only anils, the phosphorus taking the



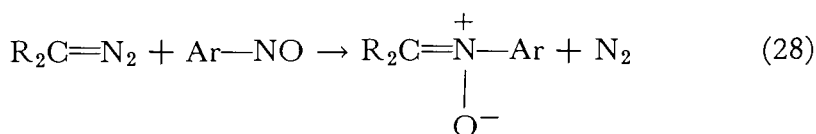
oxygen^{65, 66} (Eq. 26), in analogy with the Wittig olefin synthesis.

ALKYLATING AGENTS In view of the low basicity of nitroso compounds, it is not surprising that they should ordinarily be inert to alkylating agents. *Bis*(α -nitrosotoluene) reacts with benzyl chloride in the presence of sodium ethoxide,⁶⁷ but the products are the N- and O-benzyl derivatives of benzaldoxime, into which the nitroso dimer is probably first converted by the strong base. Nitrobenzyl chlorides, however, react readily with nitrosobenzenes in the presence of strong base to give nitrones in high yields⁶⁸ (Eq. 27). The necessity for both nitro groups and very strong



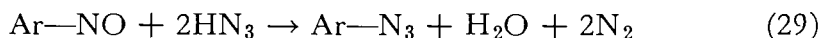
base suggests that this is not a simple alkylation, but is an analog of the Kroehnke reaction and proceeds by way of a nitrobenzyl carbanion.

DIAZOALKANES Diazoalkanes react with nitroso compounds similarly to the nitrobenzyl chlorides, giving nitrones^{65, 69} (Eq. 28). This reaction,



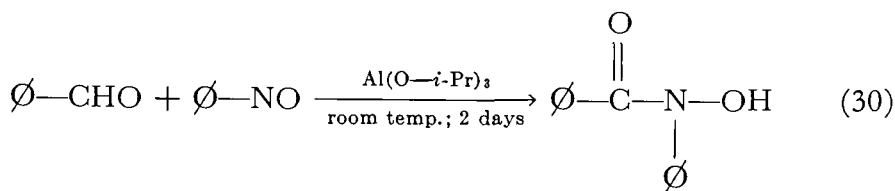
which proceeds rapidly and spontaneously at room temperature without catalysis, probably involves electrophilic attack by the nitroso nitrogen on the diazoalkane carbon (cf. Chapter 10). When diazomethane is used, further oxidation takes place, giving nitrones derived from glyoxal ($\text{ArN}(\text{O})=\text{CH}-\text{CH}=\text{N}(\text{O})\text{Ar}$) rather than from formaldehyde.

HYDROGEN AZIDE The reaction of nitrosobenzenes with hydrogen azide is perhaps at first parallel to the reaction with diazoalkanes; the presumed intermediate, $\text{Ar}-\text{N}(\text{O})=\text{NH}$, would be expected to react further with the acidic reagent, giving a diazonium azide. The actual products are, indeed, aryl azides⁷⁰ (Eq. 29), which are formed rapidly from diazonium azides (cf. Chapters 10 and 11). Reaction is spon-

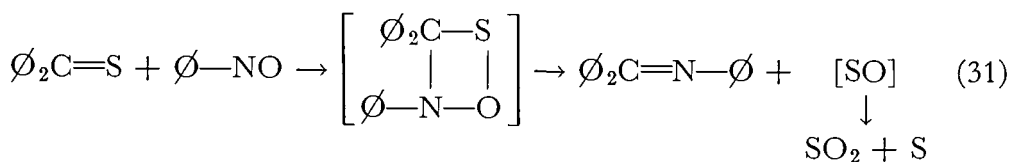


taneous, nitrogen evolution is generally quantitative, and electron-withdrawing substituents promote the reaction⁷¹ (*p*-dimethylaminonitrosobenzene, on the other hand, reacts poorly). The presumed mechanism is supported by the results of isotopic labeling experiments, which show that both N-2 and N-3 of the resulting azide are derived from the outer nitrogens of the hydrogen azide.⁷¹

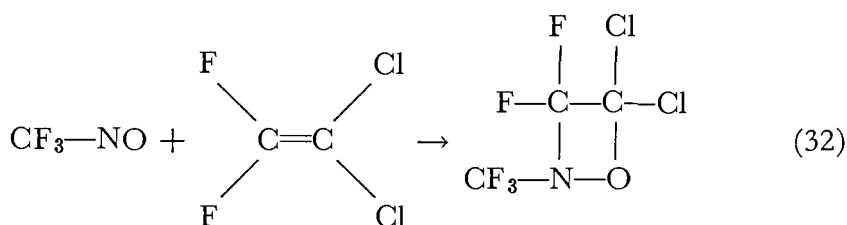
ALDEHYDES AND THIOKETONES Benzaldehyde reacts with nitrosobenzene under the conditions of the Tishchenko reaction to give N-phenylbenzohydroxamic acid (Eq. 30); the formation of benzyl benzoate is completely suppressed.⁷² The carbonyl group of ketones is unreactive



toward nitroso compounds, but thioketones are converted to anils, perhaps through formation and fragmentation of a four-membered ring⁶⁶ (Eq. 31).

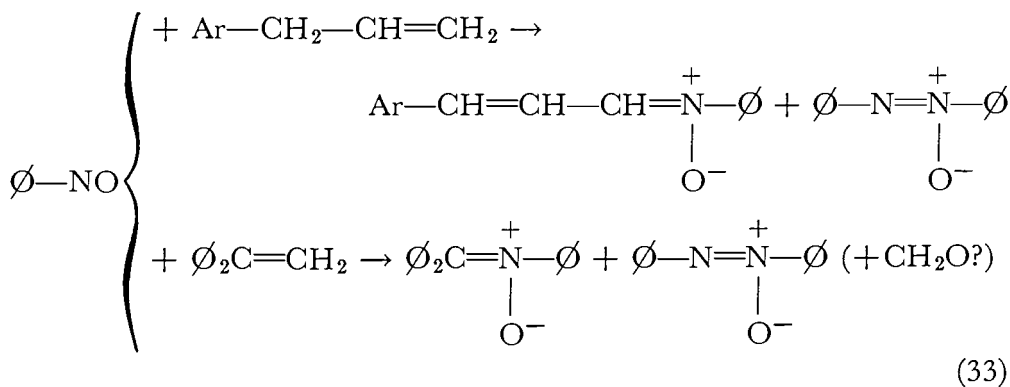


OLEFINS Nitroso compounds react with both mono-olefins and conjugated dienes and with acetylenes. Two principal types of product have been observed from mono-olefins: oxazetidines, resulting from cycloaddition ⁷³ (Eq. 32), and nitrones, resulting from addition with or without

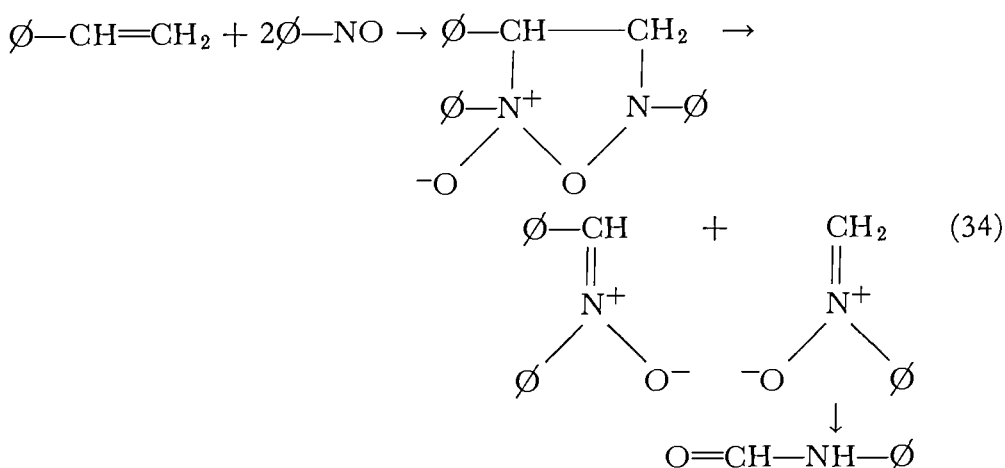


concomitant oxidation or carbon-skeleton cleavage. Copolymerization with olefins has also been observed.⁷³ Only certain highly fluorinated ethylenes have been found to give oxazetidines; earlier claims to have obtained them from other olefins have been shown to be erroneous.⁷⁴

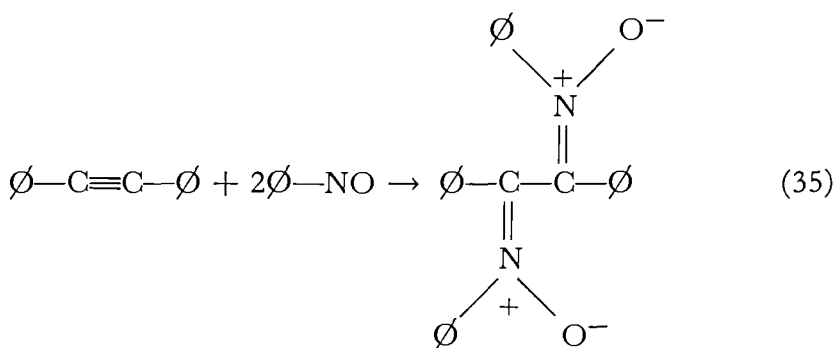
The reaction of simple aliphatic mono-olefins has not yet been properly elucidated, and our knowledge of the nitrosobenzene-olefin reaction is largely confined to aryl-substituted olefins. 3-Aryl olefins (i.e., allyl-benzenes) react at the 1-position, giving N-phenyl nitrones derived from cinnamaldehydes ⁷⁵ (Eq. 33); the oxidation that leads to the new ethylenic



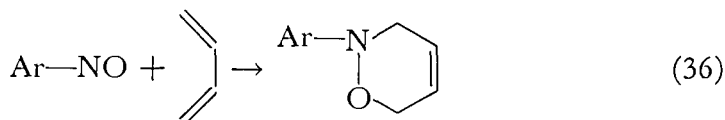
double bond does not occur when *p*-dimethylaminobenzaldehyde is used.^{76, 77} Styrene,⁷⁸ 1,1-diphenylethylene,⁷⁴ and other 1-arylethylenes ⁷⁵ give nitrones derived from cleavage at the double bond (Eq. 33). The mechanism has been partly elucidated in the case of styrene, which first forms an isolable but unstable 1:2 adduct, probably of tetrahydrofuroxan structure ⁷⁸ (Eq. 34).



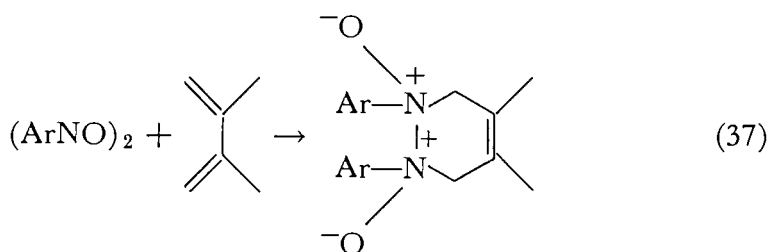
A variety of acetylenes have been found to react with nitrosobenzene, although acetylene itself is inert. Toluene gives a *bis*-nitrone derived from benzil (Eq. 35), but in other instances the reaction may be more complex.⁷⁹ Quinone also gives a vicinal dinitrone.⁷⁶



Conjugated dienes undergo the Diels-Alder reaction with monomeric nitroso compounds, giving dihydro-1,2-oxazines⁸⁰ (Eq. 36). The reaction obeys second-order kinetics, with a rather low activation energy

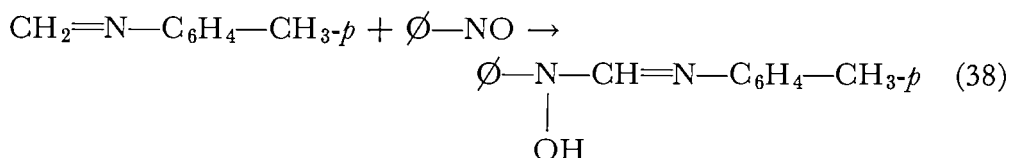


(12–15 kcal/mole).⁸¹ Unsymmetrically substituted dienes sometimes give mixtures of isomers, but 1-arylbutadienes always give exclusively the isomer with oxygen attached to the benzylic carbon.⁸⁰ The dimers of nitroso compounds are also capable of Diels-Alder addition, as shown by the example of *p*-nitronitrosobenzene and 2,3-dimethylbutadiene⁸² (Eq. 37).



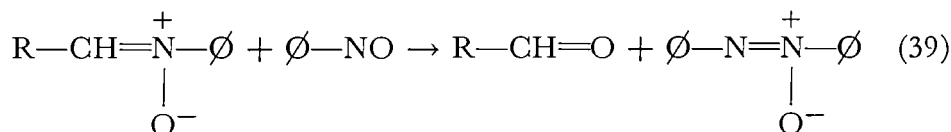
Diphenylketene reacts readily with nitrosobenzene, giving four-membered-ring products.⁸³

KETIMINES AND ALDIMINES Ketimines are evidently inert to nitrosobenzenes, since they are in many instances formed in good yield from reactions of the latter. Formaldehyde anils, however, react readily; N-hydroxyformamidines are formed⁸⁴ (Eq. 38), contrary to earlier reports



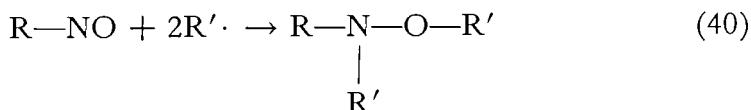
that the products had the oxazetidine structure.

N-Phenyl nitrones are sometimes cleaved by nitrosobenzene to the corresponding carbonyl compound and azoxybenzene^{75a} (Eq. 39); the reaction is evidently slow, but is probably significant in sapping the yields



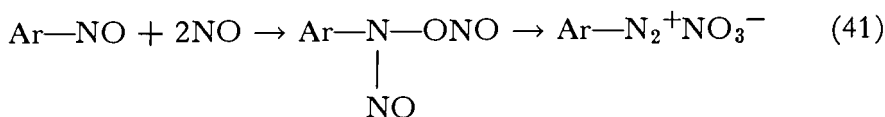
of nitrones formed by reactions starting with nitroso compounds.

FREE RADICALS Nitroso compounds are outstandingly reactive toward free radicals and are of use as radical traps and polymerization inhibitors. In general, two molecules of radical are consumed, giving rise to fully substituted hydroxylamines⁸⁵⁻⁸⁷ (Eq. 40). The "methyl affinity" of

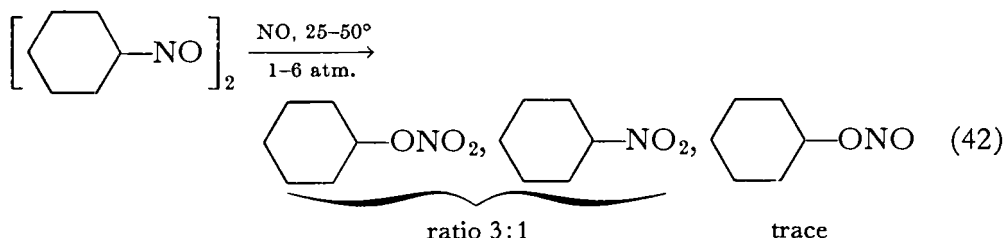


nitrosobenzene, for example, is exceptionally high (*ca.* 10^5). An important example of reactions of this kind is that with nitric oxide, which gives diazonium nitrates⁸⁸ or their expected decomposition products, presum-

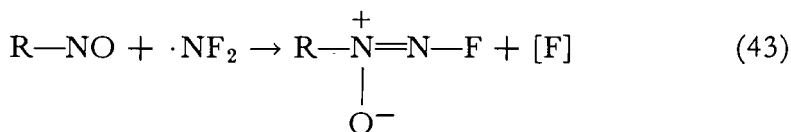
ably via an O,N-dinitrosohydroxylamine (Eq. 41). With trifluoronitrosomethane at -100° , the initial dinitrosohydroxylamine can indeed be



isolated.³² With aliphatic nitroso compounds, the products usually isolated are the corresponding nitroalkane and nitrate ester^{25, 89} (Eq. 52). Nitrous acid can bring about the same reaction.⁹⁰

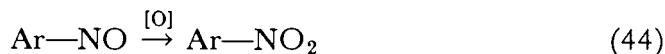


Difluoramine radicals convert monomeric aliphatic and aromatic nitroso compounds to N-fluoro azoxy compounds smoothly at room temperature (Eq. 43); the extra fluorine is found as fluorinated by-products.⁹¹



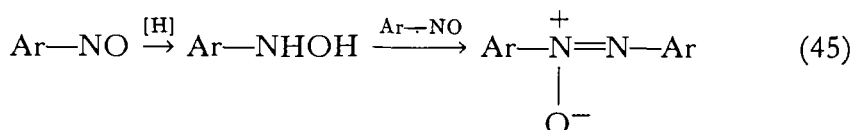
Difluoramine brings about the same reaction.

OXIDATION Nitroso compounds are in general oxidizable to the corresponding nitro compound (Eq. 44), but most of the reported studies

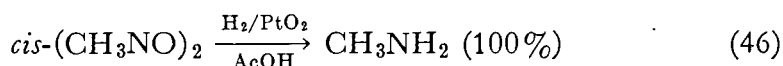


have been concerned with aromatic nitroso compounds. Nitric acid, alkaline hydrogen peroxide, and permanganate have been used with success.⁹² Various peroxy acids also oxidize nitroso compounds to nitro compounds; Caro's acid (H_2SO_5) has been most widely used, but peroxytrifluoroacetic acid is also very effective.³⁸ It appears that the greater the acidity of the peroxy acid, the more rapid its oxidizing action on nitroso compounds, a fact that suggests nucleophilic displacement on oxygen as the rate-determining step.⁹³ The rate law, first order each in peroxy acid and nitroso compound, is consonant with this view, as is the negative sign of the reaction parameter in the Hammett equation for the oxidation of *para*-substituted nitrosobenzenes.⁹³

REDUCTION Monomeric nitroso compounds are very easily reduced; in fact, the inclination to reduction is so great that it is hard to avoid the formation of reduction products to some extent in most reactions of nitrosobenzenes. The first stage is formation of a hydroxylamine, but this usually condenses with more nitroso compound so fast that the product actually isolated is nearly always azoxybenzene (Eq. 45). Many common reducing agents are effective, among which may be mentioned sodium

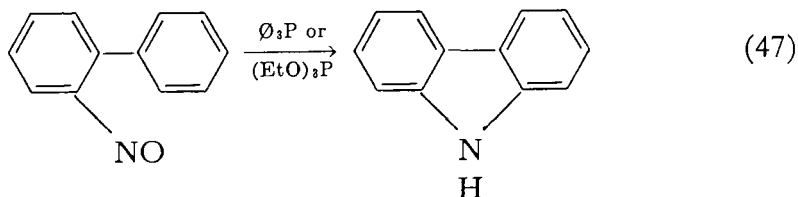


borohydride,⁹⁴ alcoholic alkali or alkoxide,^{95, 96} and arsenite.⁹⁷ Drastic reduction converts nitroso compounds to amines; stannous chloride,^{98, 99} sodium dithionite,⁴⁷ and hydrogen in the presence of a platinum catalyst^{2, 24} (Eq. 46) have been used. Bisulfite gives aniline N- and C-sulfonic acids.¹⁰⁰ Electrolytic reduction occurs so easily and with such a high po-

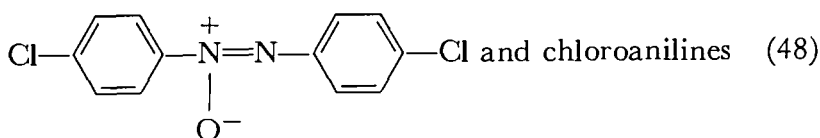
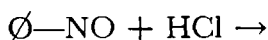


tential that a practical dry cell has been built with a nitrosobenzene cathode and a magnesium anode.¹⁰¹ One example has been reported of catalytic hydrogenation of an aliphatic nitroso dimer to a hydroxylamine (cyclohexylhydroxylamine, 58%).^{53a} Further information on the intermediate stages of reduction of nitroso compounds may be found in Chapter 14.

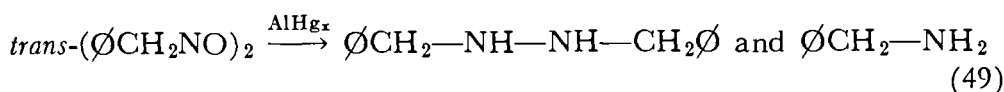
The first detectable stage in the reduction of nitroso compounds is the formation of a radical-anion, $\text{R}-\text{NO}^-$; this is produced by certain anionic reagents,^{100, 102} particularly mercaptides, and has been termed "moderately stable," even though not isolated.¹⁰² Some reagents, notably trivalent phosphorus compounds, such as triphenylphosphine and sodium dithionate, appear to accomplish removal of an oxygen atom as the first stage. The azoxy compounds that are usually formed¹⁰³ perhaps arise from combination of the deoxygenated fragment with another molecule of nitroso compound; *o*-nitrosobiphenyl, however, undergoes cyclization to carbazole instead¹⁰⁴ (Eq. 47). Hydrogen chloride accomplishes



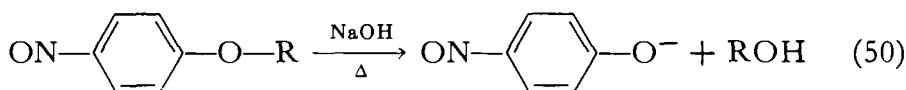
chlorinative reduction in some instances¹⁰⁵ (Eq. 48).



There are some instances of reduction that seem very probably to involve direct reduction of nitroso dimers. Deoxygenation to azoxy or azo compounds has been observed with triphenylphosphine¹⁰³ and catalytic hydrogenation,^{53a} and several examples of the formation of hydrazines from the more stable aliphatic nitroso dimers (Eq. 49) have been reported.^{7, 53a}



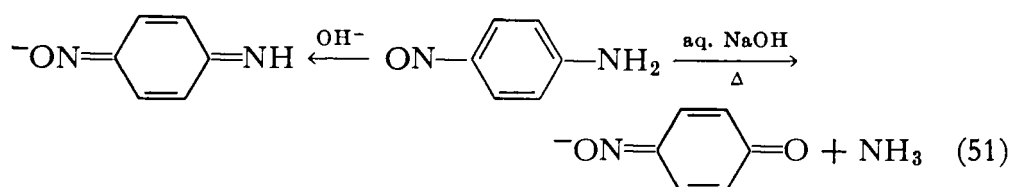
NUCLEAR REACTIONS OF NITROSOBENZENES. The effect of a nitroso group on the reactivity of the benzene ring and its attached substituents is not without interest. The nitroso group is electron-withdrawing and labilizes para substituents toward displacement by nucleophilic reagents. *p*-Nitrosophenyl ethers, for example, are cleaved by hot alkali to *p*-nitrosophenol¹⁰⁶ (Eq. 50), and the similar cleavage of *p*-nitrosodialkylanilines



to give a dialkylamine¹⁰⁷ is a venerable textbook reaction. It is worthy of note that this reaction proceeds best with aqueous alkali, for alcoholic alkali causes reduction of the nitroso group to become a serious competitor. The electron-withdrawing effect of the nitroso group is apparently not large, however, for the base strength of *p*-nitrosodimethylaniline ($\text{pK}_a = 4.0$ in water, 3.52 in 50% alcohol¹⁰⁸) is only 1 power of 10 less than that of dimethylaniline. Substitution reactions on the ring of nitrosobenzenes by electrophilic reagents would be expected to give *meta*-oriented products. The fact that such reactions as bromination give instead *ortho* and *para*-substituted products, a source of misunderstanding for many years, was finally revealed⁸ as the result of the intermediacy of an adduct, $\text{ArNO} \cdot \text{HX}$. Indeed, bromination of nitrosobenzene is autocatalytic, the hydrogen bromide concomitantly produced accelerating the reaction.

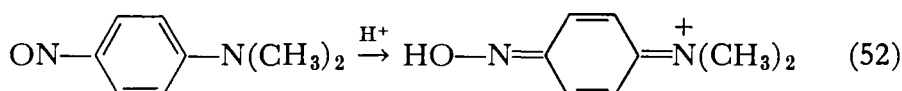
The behavior of *o*- and *p*-nitrosoanilines and phenols requires separate discussion. *p*-Nitrosoaniline is a blue substance that shows most of the reactions typical of nitroso compounds. It is, however, capable of forming salts with aqueous bases as well as acids, and hot alkali hydrolyzes

it to ammonia and a salt of quinone monoxime (Eq. 51). These facts

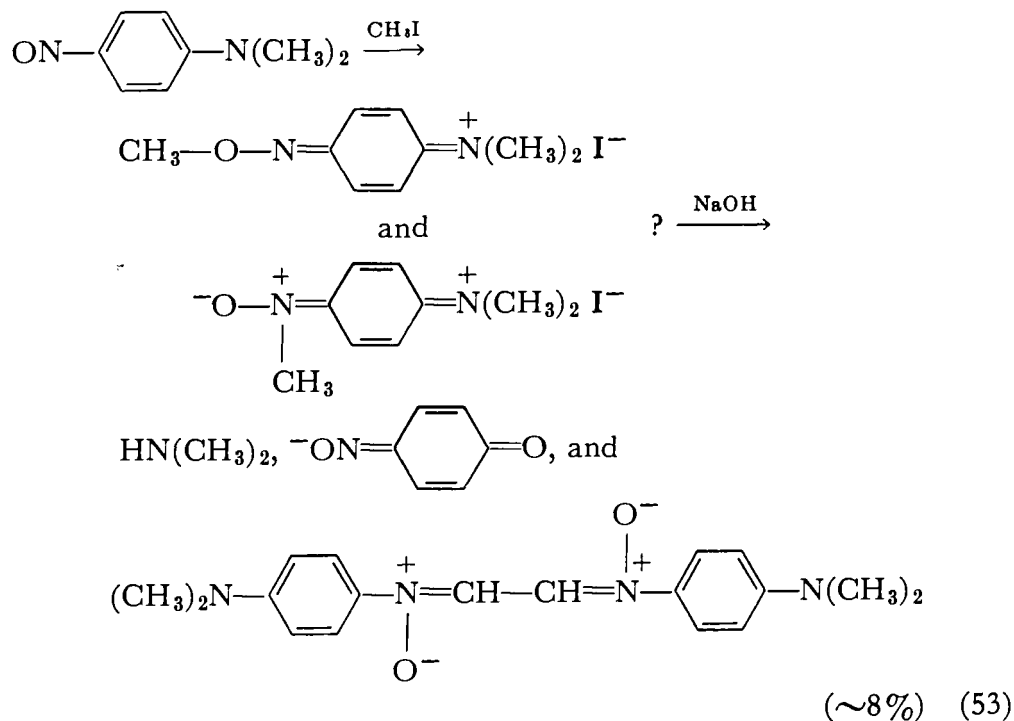


suggest (but do not require) a tautomeric equilibrium between the nitrosoaniline and the quinone oxime imine structures, with an equilibrium position perhaps strongly favoring the former. Similar remarks apply to the N-alkyl nitrosoanilines.

The salts of the nitrosoanilines with acids no longer have the green color typical of nitroso compounds, but are orange-yellow. Protonation at the nitroso oxygen (Eq. 52) provides a reasonable explanation, for

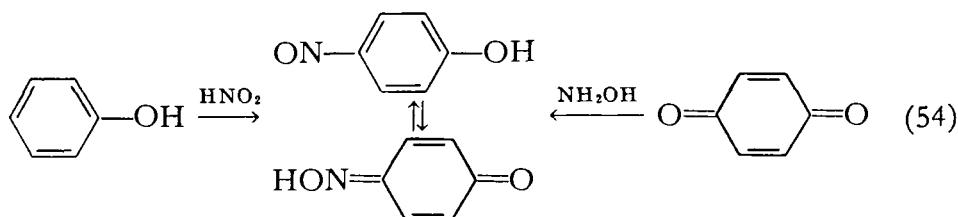


the resulting structure is a quinone derivative and not a nitroso compound. Some questionable support for this view is found in the behavior of nitrosoanilines toward alkylating agents. *p*-Nitrosodimethylaniline reacts with methyl iodide to give a brown substance, whose structure has been inferred to be that of a quinone oxime derivative on the basis of its hydrolysis to dimethylamine^{109, 110} (Eq. 53). The evidence for the structure lacks conviction, but the assumed structure is in accord with the fact that

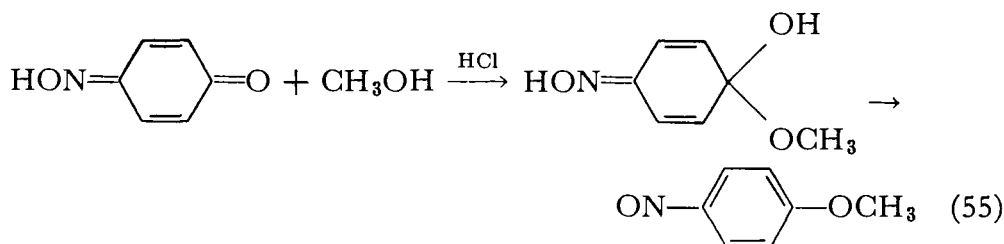


nitrosoanilines are vinylogs of nitrosamines, which also undergo alkylation on oxygen (cf. Chapter 15).

Nitrosophenols exhibit ambivalent behavior analogous to that of the nitrosoanilines, but the evidence for a true tautomeric equilibrium is clearer. The same substance is obtained by nitrosating phenol or by treating quinone with hydroxylamine (Eq. 54). It can be obtained in



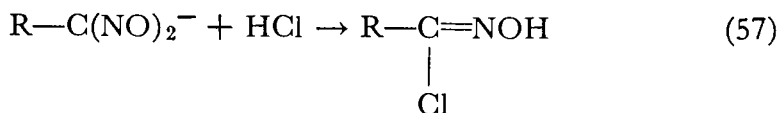
two crystalline forms, one of which is pale green, the other nearly colorless; the two forms give identical solutions, whose color varies from light green (ether, water, alcohol) to yellow (benzene, chloroform). The electronic spectra ^{111, 112} of solutions of "*p*-nitrosophenol" when compared with those of *p*-nitrosoanisole and quinone O-methylmonoxime indicate that the quinone oxime tautomer predominates, and that the nitrosophenol tautomer is definitely present, but in a proportion less than 15%. An interesting feature of *p*-nitrosophenols is that they are converted to nitrosophenyl ethers simply on standing in alcohol solution in the presence of a trace of acid ¹¹²; this reaction presumably takes place through hemiacetal formation at the quinone oxime carbonyl group (Eq. 55).



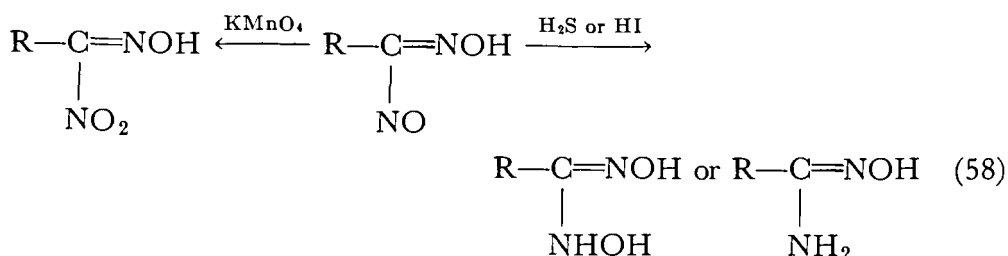
NITROSOLIC ACIDS The chemistry of the little-known nitrosolic acids is in many ways similar to that of ordinary nitroso compounds, but in some ways is individual. Formonitrosolic acid when liberated from its salts by excess mineral acid fragments to fulminic acid and nitroxyl ¹¹³ (Eq. 56); the higher nitrosolic acids fragment to nitriles. Aqueous



hydrochloric acid, however, has been reported to give hydroximoyl chlorides ¹¹⁴ (Eq. 57). Reduction, which is accomplished easily by such



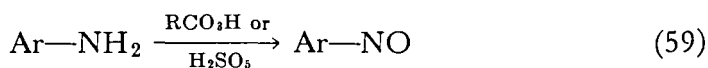
reagents as hydrogen sulfide or hydriodic acid, converts nitrosolic acids



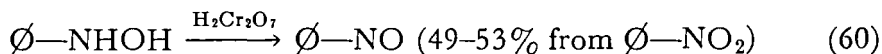
to hydroxyamidoximes or amidoximes¹¹⁴ (Eq. 58). Oxidation by permanganate gives nitrolic acids¹¹⁵ (Eq. 58).

PREPARATIVE METHODS

Oxidation of primary amines is a widely used preparative method for aromatic nitroso compounds; it is less general but sometimes successful with aliphatic primary amines. Caro's acid (H_2SO_5 , prepared from ammonium peroxydisulfate and concentrated sulfuric acid)^{13b, 32} has been the most common oxidizing agent, but peroxyacetic acid^{116, 53a} and hydrogen peroxide in acetic acid¹¹⁷ have also been used with good results (Eq. 59). Further oxidation to nitro compounds is always a possibility, as discussed in the foregoing section, but is usually more difficult. Only



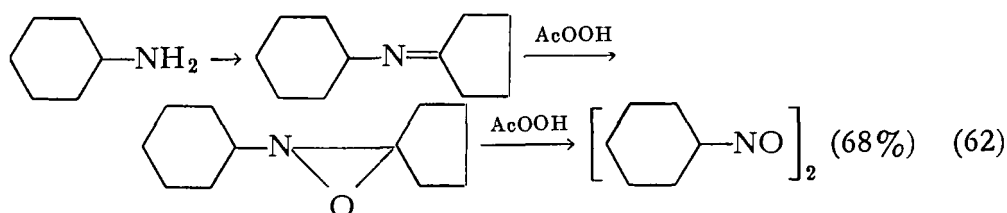
rarely have oxidizing agents other than peroxides, such as permanganate in the presence of formaldehyde, which converts cyclohexylamine to nitrosocyclohexane in over 80% yield,¹¹⁸ been successfully employed.



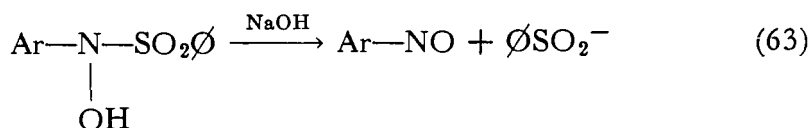
Oxidation of hydroxylamines to nitroso compounds (Eqs. 60, 61) is a much easier reaction, but is limited as a preparative method by the accessibility of the required hydroxylamines; the latter, however, are in many cases easily available by reduction of nitro compounds. Chromic acid is perhaps the reagent of choice,¹¹⁹ but other agents, such as periodic acid² or air,^{53a, 120} have been used successfully. The oxidation of N-nitrosohydroxylamines also leads to C-nitroso compounds,^{13b, 121} but appears to have no preparative advantages.

Although the oxidation of aliphatic primary amines is only occasionally of preparative value, the indirect route involving conversion to a ketimine and oxidation (via an oxaziridine) appears to be general and reliable¹¹⁷

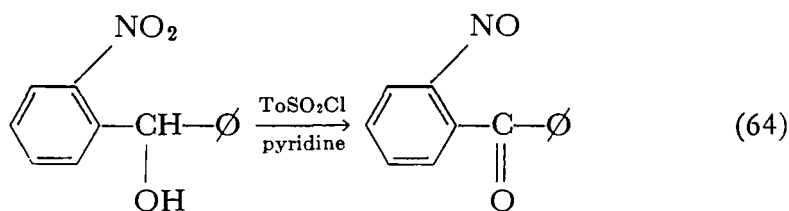
(Eq. 62). The net result of oxidation can be accomplished by an elimi-



nation reaction with N-substituted sulfonylhydroxamic acids ¹²² (Eq. 63), a process that might have utility in special circumstances.

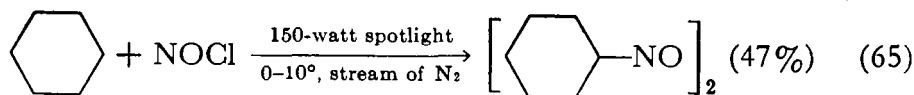


Reduction of nitro compounds is very seldom of preparative value for nitroso compounds, owing to the difficulty of halting the reduction. Small but usable yields have been obtained with *o*- and *p*-dinitrobenzene by reduction with hydroxylamine or stannite and methanolic alkali, however.¹²³ Internal oxidation-reduction may be more successful, as illustrated by the conversion of *o*-nitrobenzhydrol to *o*-nitrosobenzophenone ¹²⁴ (Eq. 64). This reaction is believed to occur through cycliza-



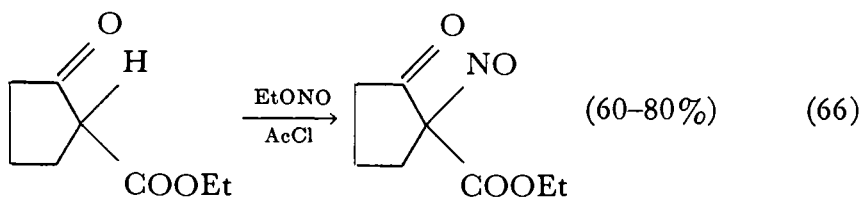
tion of the tosylate ester to a benzisoxazoline derivative, followed by fragmentation of the heterocyclic ring.

There are several ways by which a nitroso group can be introduced directly into a molecule. The free-radical reaction of nitrosyl chloride (or a mixture of chlorine and nitric oxide) with saturated hydrocarbons leads to nitrosoalkanes in good yield, but as a preparative method suffers from lack of selectivity. Cyclohexane, however, in which all positions are alike, gives nitrosocyclohexane in good yield ^{3, 17} (Eq. 65). Ionic nitrosation requires an activated site, such as found in active methylene

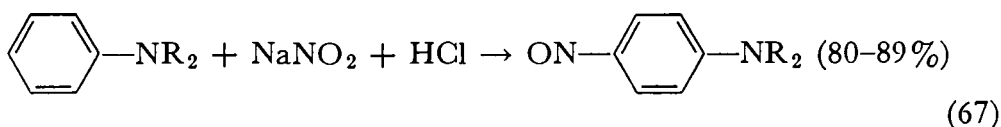


compounds. Nitrosation of such substances with nitrites or nitrous acid under strongly basic or acidic conditions, as usually conducted, leads to oximes in good yield,¹²⁵ but conditions more nearly neutral are necessary if the intermediate C-nitroso compound is to resist isomerization. Such

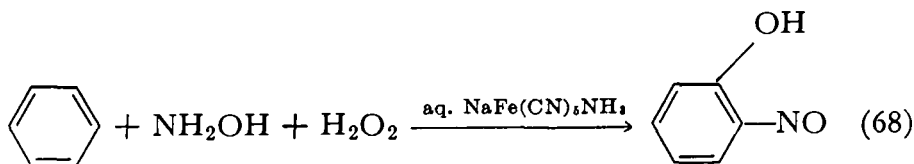
conditions are provided by the use of "nitrous fumes" (essentially N_2O_3) in ether, or ethyl nitrite and acetyl chloride ¹²⁵; several α -nitroso- β -dicarbonyl compounds have been made in this way, such as 2-nitroso-2-carboethoxycyclopentanone ¹²⁶ (Eq. 66).



Ionic nitrosation is also a successful way of introducing a nitroso group into highly activated aromatic rings; for preparative purposes, this method is limited to phenols, naphthols, and secondary and tertiary anilines and naphthylamines. N-Monoalkylanilines must generally be nitrosated in two stages, for the immediate product is the nitrosamine, which rearranges slowly in contact with acid to the ring-substituted isomer (Fischer-Hepp rearrangement; see Chapter 15). N,N-Dialkylanilines are generally easily nitrosated, although the reaction becomes more difficult and may in extreme cases be prevented altogether in the presence of bulky substituents.^{127, 128} Detailed directions for the nitrosation of thymol,¹²⁹ β -naphthol,¹³⁰ and dimethyl- and diethylaniline ¹³¹ (Eq. 67) are available in *Organic Syntheses*. *o*-Nitrosophenols are available directly from the



corresponding hydrocarbon by an oxidative nitrosation process whose mechanism remains obscure, but which has been suggested to involve attack by nitroxyl, HNO (Baudisch reaction).^{132, 133} The reagents are hydrogen peroxide, hydroxylamine, and a complex salt catalyst, such as sodium pentacyanoammineferroate, and the reaction takes place smoothly at room temperature in an aqueous medium (Eq. 68). The nitrosation of phenols in the *ortho* position can be accomplished under similar con-



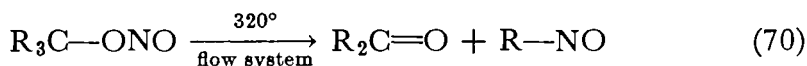
ditions; the use of a copper salt as a catalyst results in *ortho* orientation apparently through formation of a chelate complex.¹³³ Although many *o*-nitrosophenols have been prepared by these reactions, the published reports are deplorably lacking in experimental detail.

Grignard reagents can be used as sources of both aliphatic ¹³⁴ and aromatic ¹³⁵ nitroso compounds by reaction with nitrosyl chloride (Eq. 69).

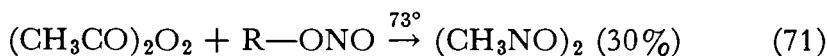


Organomercury compounds can also be used ^{136, 137} in reaction with either nitrosyl chloride or nitrogen tetroxide.

Nitrite esters can be utilized as sources of nitroso compounds by either photolysis, thermolysis, or reaction with diacyl peroxides. The photolytic reaction has been the most thoroughly studied with cycloalkyl nitrites, which undergo ring cleavage to give ω -nitroso aldehydes for ring sizes 4 to 6 atoms, or transannular nitrosation to give nitrosocycloalkanones for larger rings ¹³⁸ (see Chapter 15). Thermolysis of open-chain alkyl nitrites (Chapter 15) has been used successfully for the preparation of a number of nitrosoalkane dimers ¹⁴ (Eq. 70); the products must be first quenched in a cold trap to prevent isomerization of the monomers to

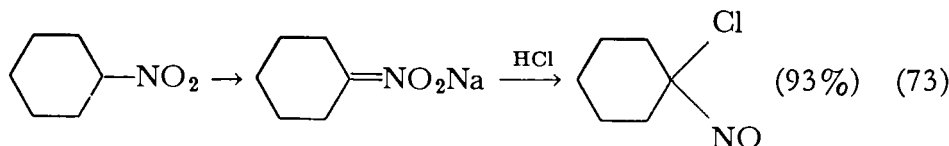
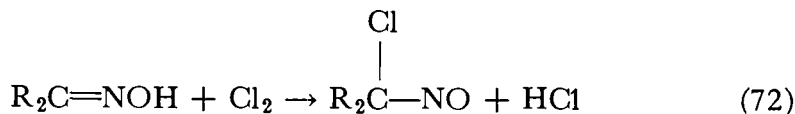


oximes. The largest alkyl group migrates to nitrogen preferentially; although yields have not been reported, the method appears to be of real preparative value. The reaction of acetyl peroxide with boiling butyl or amyl nitrite has been used to prepare nitrosomethane dimer ²³ (Eq. 71); in this case, the methyl group does not come from the nitrite ester,

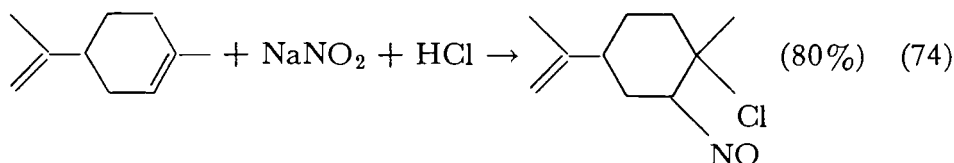


obviously.

Some specifically substituted aliphatic nitroso compounds are prepared by special reactions that introduce both the nitroso group and the substituent. α -Chloro nitroso compounds, for example, can be prepared by chlorination of oximes ¹³⁹ (Eq. 72), or by treatment of salts of nitroalkanes with ethereal hydrogen chloride ¹⁴⁰ (Chapter 14) (Eq. 73). β -Chloro nitroso compounds, commonly called nitroso chlorides, can be

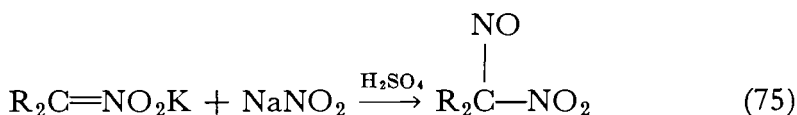


prepared by the addition of nitrosyl chloride to olefins ^{98, 141} (Eq. 74). It is not necessary to use preformed nitrosyl chloride; the simultaneous

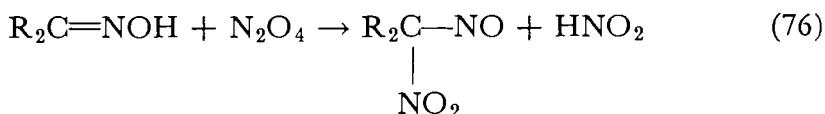


addition of concentrated hydrochloric acid and saturated sodium nitrite to a solution of the olefin in isopropyl alcohol gives good yields of nitroso chlorides.¹⁴² The reaction is in general ionic, and the positions taken by the entering groups can be predicted by Markovnikov's rule, the stereochemical course of the addition being *trans*. Strained double bonds of the norbornene type have been found to undergo *cis* addition of nitrosyl chloride, however.¹⁴³

α -Nitro nitroso compounds (pseudonitroles) can be obtained either by nitrosation of salts of *sec*-nitroalkanes¹⁴⁴ (Eq. 75), or by the reaction

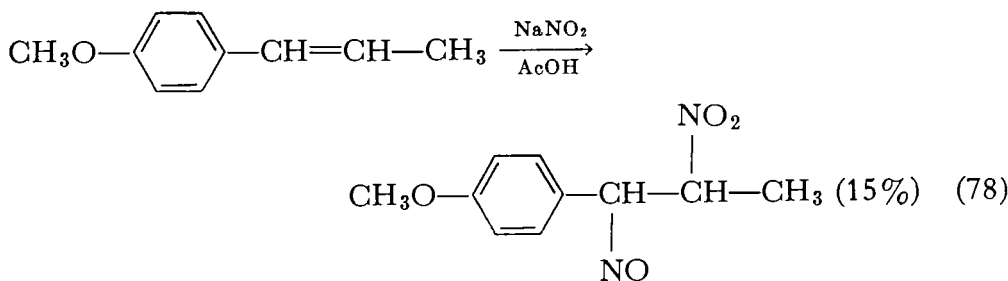
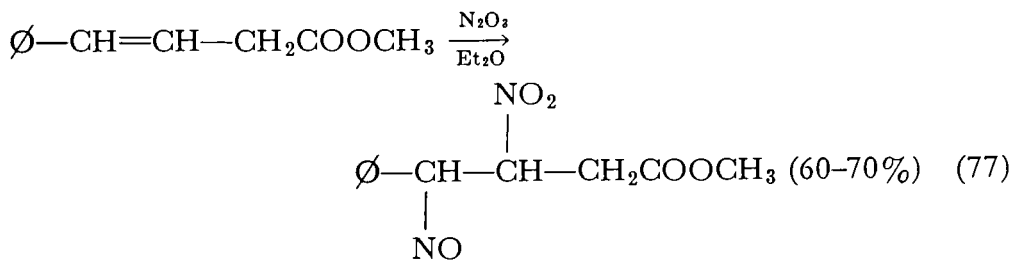


of nitrogen tetroxide with ketoximes¹⁴⁵ (Eq. 76) (Chapter 8). The same

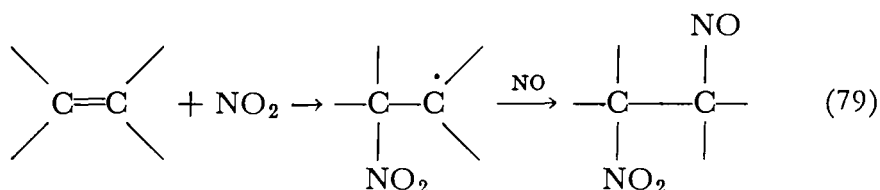


result has in some instances been obtained from treatment of oximes with nitrous acid,¹⁴⁶ but the reaction more often takes a different course (see Chapter 8).

β -Nitro nitroso compounds (pseudonitrosites or nitrosites) are generally available by the reaction of "nitrous fumes" (essentially N_2O_3 in equilibrium with NO and NO_2) with olefins¹⁴⁷ (Eqs. 77, 78). Although

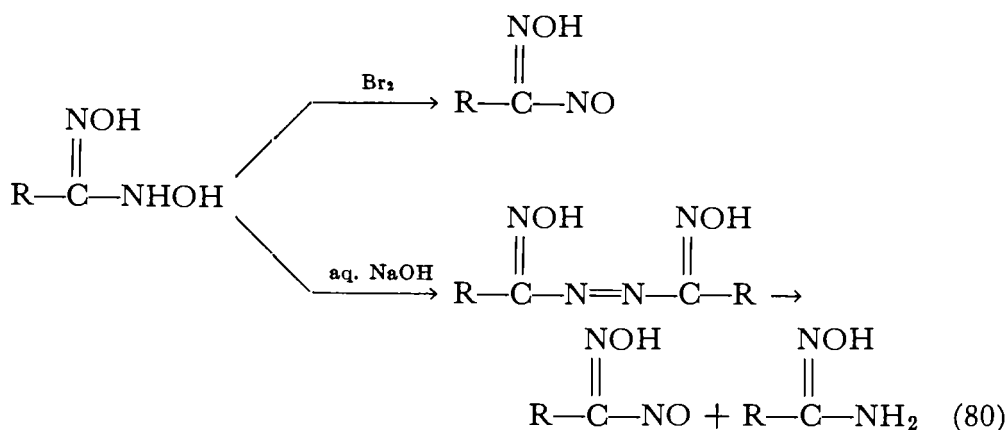


the yields may be good, they are more often low; nevertheless, the reaction has been of considerable value in the study of terpenes,¹⁴⁸ for it affords crystalline derivatives that can be used for identification and can be degraded for structure proof. The reaction is apparently a free-radical one, and the position taken by the nitroso and nitro groups cannot be predicted by Markovnikov's rule. It has been proposed¹⁴⁹ that the first step is addition of nitrogen dioxide to give a β -nitroalkyl radical, which then combines with nitric oxide (Eq. 79). It should be noted that



nitric oxide or nitrogen dioxide by themselves also react with olefins, but the products are largely nitro compounds.^{40, 149}

Nitrosolic acids are prepared by the oxidation of hydroxyamidoximes¹⁵⁰ (Chapter 8) or by their disproportionation in alkali¹⁵¹ (Eq. 80),



by the spontaneous decomposition of N-nitrosohydroxyamidoximes,¹⁵⁰ and by reduction of nitrolic acids with sodium amalgam.¹⁵⁰

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chapter
fourteen

C-Nitro Compounds

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NOMENCLATURE

Nitro compounds, both aliphatic and aromatic, are named only by use of the prefix "nitro-" together with a suitable locant, as in "*p*-nitrotoluene" and "2-nitropropane"; a suffix form is not available. Two compounds, trinitromethane (nitroform) and trichloronitromethane (chlorpicrin) are commonly called by their trivial names. α -Nitroso nitroalkanes bear the class name pseudonitrole, and α -hydroximino nitroalkanes are called nitrolic acids, as in "acetonitrolic acid," $\text{CH}_3\text{—C(=NOH)NO}_2$.

The enol-type tautomers of nitroalkanes, $\text{R}_2\text{C=NO}_2\text{H}$, are named according to both *Chemical Abstracts* and IUPAC rules by use of the prefix "*aci*-nitro-" as in "*aci*-nitroethane," $\text{CH}_3\text{CH=NO}_2\text{H}$, but alternative names based on the prefix "isonitro-" or the suffix "-nitronic acid" have a long history of use. Unfortunately, the latter have more often than not been used in the form "ethylnitronic acid" (for the preceding compound), which is misleading because there is actually no ethyl group, or in the additive form "ethanenitronic acid," which is superficially analogous to "ethanesulfonic acid," but hides the presence of a double bond.

The form "ethylidenenitronic acid" is free of these objections and allows the closely related compounds R_2NO_2H to be named in parallel fashion, as dialkylnitronic acids; otherwise, they must be named as dialkylhydroxylamine N-oxides.

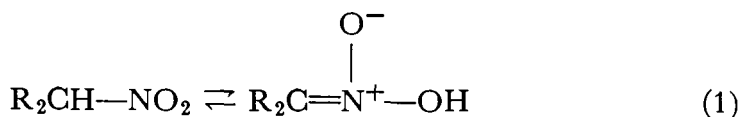
Salts and esters of nitroalkanes are named in the form "*aci*-nitroalkane, sodium derivative" by *Chemical Abstracts*, and "—, sodium salt" according to the *IUPAC Tentative Rules*; the O-alkyl derivatives, or esters, are named analogously. The foregoing rules notwithstanding, those who publish in the field predominantly prefer to name salts and esters as metal or alkyl nitronates.

PROPERTIES ^{1, 2}

The simple nitroalkanes and nitroarenes are colorless liquids when pure and quite dry, although they are usually encountered with a straw to yellow tint. Nitromethane, bp 101°, fp -28°, and nitrobenzene, bp 211°, fp 5.7°, are both more than 10% denser than water. Nitroethylene is a very pale yellow oil, bp 98.5°, with an irritating odor and a tendency to polymerize readily. Nitromethane is soluble in water to the extent of 10% at room temperature and in turn dissolves 2% of water; it is miscible with nearly all organic solvents except saturated hydrocarbons. Nitrobenzene is soluble only to the extent of 0.2% in water.

All degrees of nitrosubstituted methane are known: dinitromethane, a colorless, unstable oil with a sharp odor, insoluble in water; trinitromethane, mp 22–23°, bp 48°/17 mm., slightly soluble in water; tetranitromethane, mp 13°, bp 124–125°/750 mm. with slight decomposition, insoluble in water. Nitrobenzenes, however, are known only up to the tetranitro stage: 1,2,3,5-tetranitrobenzene, yellowish, mp 125–126°; 1,2,4,5-isomer, bright yellow, mp 188°. 1,3,5-Trinitrobenzene, mp 122°, is an explosive sometimes known as TNB.

Nitroalkanes that bear an α -hydrogen take part in a tautomeric equilibrium with an *aci*-nitro form (nitronic acid) (Eq. 1), in which the



nitro form is considerably more stable. Equilibration is slow enough that the *aci*-nitro component can be estimated by titration with bromine,^{3, 4} in much the same way as enols can be determined in the presence of their keto tautomers. The equilibrium ratio, $K_i = [R_2C=NO_2H]/[R_2CHNO_2]$, for nitromethane is only 1.1×10^{-7} at room temperature;

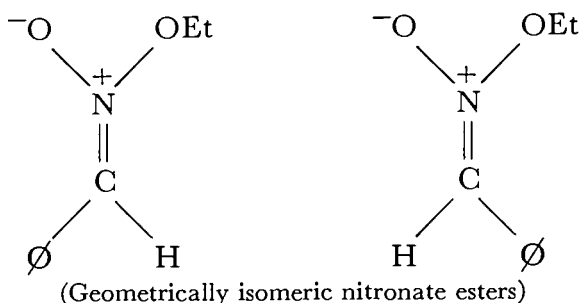
successive alkyl substitution increases the ratio significantly, although it remains small ³ (see Table 14-1). Accumulation of nitro groups on the same carbon further increases the proportion of the *aci*-nitro form; 1,1-dinitroethane, $K_i = 4 \times 10^{-2}$, exists to an extent of about 4% in the *aci*-form.^{3b}

It has been argued ⁴ that the aforementioned tautomeric equilibration cannot be real, inasmuch as ether solutions of certain nitro compounds are indefinitely stable, whereas the corresponding nitronic acids decompose in a few days in ways other than reversion to the nitro structure. This argument is not valid for several reasons: solutions of nitronic acids are enormously more acidic than those of the nitro compound, thus greatly promoting acid-catalyzed reactions; bimolecular reactions of the nitronic acid form would be kinetically favored by a factor of 10^6 to 10^{14} in *ca.* molar concentrations compared to concentrations in equilibrium with the nitro forms (cf. the values of K_i , Table 14-1); and the nitronic acid provides a hydroxylic environment that is effectively absent in solutions of the nitro compound. Furthermore, tautomerization is very slow in the absence of an acid or base as catalyst.

The nitronic acid tautomers can in some instances actually be isolated; isolation is not accomplished by actual separation of an equilibrium mixture, however, but by direct preparation of the nitronic acid by a suitable reaction (cf. Preparative Methods), commonly acidification of a nitronate salt. An unstable substance melting at 60–70° with violent decomposition has been tentatively identified ⁵ as ethylidenenitronic acid; dinitromethylenenitronic acid has been obtained ^{6a} as a solid, mp 50°, that reverts to trinitromethane when melted or dissolved, and benzylidenenitronic acid, mp 84°, and its *p*-bromo derivative are easily precipitated from solutions of the corresponding arylnitromethane salts.^{6b} The nitronic acids have much higher melting points than nitroalkanes and are markedly more soluble in water, consequences to be expected of the presence of a hydroxyl group. They can be detected qualitatively by the red-brown colors they form with ferric chloride; nitro tautomers give no such color.^{6b} It was once thought that optical activity arising from asymmetry at the α -carbon of nitroalkanes, such as 2-nitrooctane, was retained in the corresponding nitronic acids and their salts, but the apparent experimental evidence was eventually shown to be an artifact of the unsuspected presence of alkyl nitrate in the nitroalkane sample used.⁷

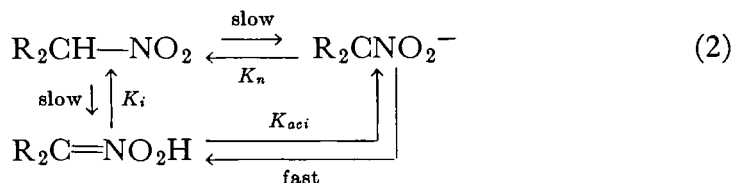
Nitronate esters, $R_2C=NO_2R$, in which the *aci*-nitro structure is fixed against tautomerism, are known in small number.⁸ Many are solids (ethyl benzylidenenitronate, for example, melts at 100–101°), apparently stable indefinitely at –78°, but most of them, especially the purely aliphatic ones, decompose slowly at room temperature. Since the nitronic acid function is unsymmetrical, geometrical isomerism should

be possible in esters having an unsymmetrical alkylidene group; isomers have indeed been identified by nuclear magnetic resonance.⁸



Dialkylnitronic acids are known so far only in the form of salts, such as sodium di-*tert*-butylnitronate,⁹ notwithstanding painstaking attempts to prepare the free acids or esters.

The topic of the acidity of nitroalkanes is complicated by their tautomerism, which, being slow, makes the nitroalkanes pseudo acids. The nitro forms react with bases only slowly, and are much weaker acids than the *aci* forms, which ionize rapidly (Eq. 2). The apparent equilibrium constant for ionization is the weighted sum of the contributions



of both forms present at equilibrium and may be represented by Equation 3. Since at equilibrium the ion product $[\text{H}^+][\text{R}_2\text{CNO}_2^-]$ must

$$K_{app} = \frac{[\text{H}^+][\text{R}_2\text{CNO}_2^-]}{[\text{R}_2\text{CHNO}_2] + [\text{R}_2\text{CNO}_2\text{H}]} \quad (3)$$

equal both $K_n[\text{R}_2\text{CHNO}_2]$ and $K_{aci}[\text{R}_2\text{CNO}_2\text{H}]$, one can solve for $[\text{R}_2\text{CNO}_2\text{H}]/[\text{R}_2\text{CHNO}_2] = K_i = K_n/K_{aci}$. Substitution in Equation 3 then leads to the relation $K_{app} = K_n/(1 + K_i)$, and both K_n and K_{aci} can be therefore evaluated from measurements of the apparent acidity constant and the equilibrium tautomer ratio. K_{aci} can also be evaluated directly by measuring the drift of the pH of solutions of nitroalkane salts that have been acidified with a mineral acid and extrapolating to zero time.

The results for some representative compounds are given in Table 14-1. It is evident that K_i for mononitroalkanes is so small that $K_{app} = K_n$ within the ordinary accuracy of measurement, and that trinitromethane is a strong acid, nearly the same as H_3O^+ . The small range of

Table 14-1 *Acidity constants and equilibrium ratios of nitroalkanes*^{3, 10, 11}

Compound	K_{app}	K_i	K_n	K_{aci}
Nitromethane	6.1×10^{-11}	1.1×10^{-7}	6.1×10^{-11}	5.6×10^{-4}
Nitroethane	3.5×10^{-9}	8.9×10^{-5}	3.5×10^{-9}	3.9×10^{-5}
1-Nitrobutane	1×10^{-10}			
2-Nitropropane	2.1×10^{-8}	2.75×10^{-3}	2.1×10^{-8}	7.7×10^{-6}
Dinitromethane	2.5×10^{-4}			
1,1-Dinitroethane	5.2×10^{-6}	4×10^{-2}	5.4×10^{-6}	1×10^{-4}
Trinitromethane	~ 0.6			
Phenylnitromethane	6.3×10^{-9}			
Ethyl α -nitropropionate	3×10^{-7}			

the values of K_{aci} is noteworthy, and the fact that methylenenitronic acid is slightly stronger than that derived from dinitroethane is remarkable and deserves reinvestigation.

The rates of tautomeric interconversion^{11, 12} and of reaction with hydroxide ion¹³ have been measured by several investigators; the latter are in the order $\text{CH}_3\text{NO}_2 > \text{EtNO}_2 > \text{PrNO}_2 > i\text{-PrNO}_2$.

Polynitrobenzenes react additively with strong bases and are thus Lewis acids. This behavior is discussed in the next section.

The basicity of nitro compounds is very low and can be detected only in such media as concentrated sulfuric acid¹⁴; nitromethane in that solvent is protonated only to the extent of 21%, nitrobenzene, 41%, as determined by cryoscopic measurements, but both are completely protonated in oleum. Crystalline addition products with Lewis acids, such as aluminum chloride, have been isolated.¹⁵

The structure of the nitro groups would be expected on the basis of nearly all valence theories to consist of a symmetrical —NO_2 group coplanar with the carbon atom to which it is attached. This means trigonally hybridized orbitals about the nitrogen and a delocalized π -orbital system encompassing the nitrogen and both oxygens, isoelectronic with the carboxylate anion. Nitromethane has been calculated from electron diffraction patterns^{16a} to have a normal C—N distance ($1.47 \pm 0.02 \text{ \AA}$), an N—O distance of $1.22 \pm 0.02 \text{ \AA}$, and an ONO angle of $135^\circ \pm 5$; there is a small barrier of 6 cal/mole to rotation about the C—N bond.^{16b}

Nitrobenzene has been examined by X-ray diffraction¹⁷ at -30° and found to have C—N = $1.486 \text{ \AA}$, N—O = $1.208 \text{ \AA}$, and an ONO angle of 124° ; the benzene ring is noticeably elongated, and the nitro group is coplanar with the ring. Nitromesitylene shows very similar distances, but the ONO angle, 117° , is somewhat smaller, and the nitro group is

rotated 66° out of the plane of the ring. The ring is considerably distorted. Other nitro compounds, such as *m*- and *p*-dinitrobenzene and 9-nitroanthracene, have also been examined by X-ray crystallography.¹⁸

Nitroalkanes absorb weakly in the near ultraviolet as a result of an $n \rightarrow \pi^*$ transition in the region 270–280 $m\mu$ and intensely near 210 $m\mu$ ($\pi \rightarrow \pi^*$).^{2, 19a} The anions, on the other hand, show only a single, intense band in the near ultraviolet, near 235 $m\mu$; *gem*-dinitro anions absorb much nearer to the visible, in the range 360–380 $m\mu$.²⁰ The absorption of nitrobenzenes^{19b} is sensitive to solvent effects, and, of course, to substitution, and reflects interaction of the nitro group with the ring; nitrobenzene itself has an intense band at 270 $m\mu$ with a pronounced inflection at about 330 $m\mu$.

The most characteristic feature of the infrared spectrum of nitro compounds is a pair of strong bands due to asymmetric and symmetric stretching of the N—O bonds.^{2, 21} They appear in the ranges 1540–1610 cm^{-1} and 1315–1390 cm^{-1} , respectively, and are generally separated by 200 to 300 cm^{-1} ; the largest separation is peculiar to 1,1,1-trinitro compounds, and that of *gem*-dinitro compounds is intermediate.² Aromatic nitro compounds absorb similarly, but in a somewhat narrower range ($1527 \pm 10 \text{ cm}^{-1}$ and $1350 \pm 10 \text{ cm}^{-1}$).²¹ Nitronate esters absorb at somewhat higher frequency (1610–1650 cm^{-1}).⁷ The anions of trinitromethane and *gem*-dinitroalkanes show neither absorption clearly attributable to C=N stretching nor that of undisturbed nitro groups, a circumstance that is consistent with the concept that the negative charge is distributed symmetrically among all nitro groups.²²

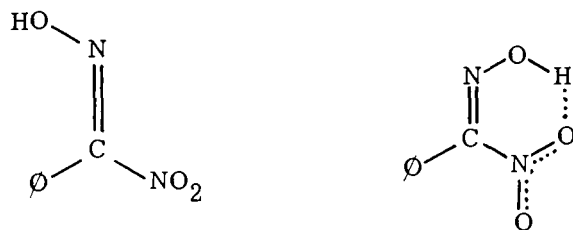
The nuclear magnetic resonance spectra of nitroalkanes reflect the strong electron-withdrawing effect of the nitro group; α -hydrogens have a downfield chemical shift of 4.28 to 4.58 ppm from tetramethylsilane.²³ The dipole moments²⁴ also reflect this effect; those of nitroalkanes are of the order 3.2 to 3.7D and that of nitrobenzene is 3.93D, raised by *p*-alkyl substitution and lowered by *p*-chloro substitution. That of nitrodurene is somewhat lower (reported values 3.42–3.62D), probably as a result of steric inhibition of conjugation through twisting of the nitro group out of the plane of the ring. The results of such a steric effect are also observed in many other properties of aromatic nitro compounds, particularly spectrographic properties.^{18c, 25}

The dielectric constants of both nitromethane (~ 38) and nitrobenzene (~ 35) are high; these substances are accordingly fair ionizing solvents and dissolve many salts. Tetranitromethane, however, has a low dielectric constant (~ 2).

The electronic properties of the nitro group as a substituent are of particular interest because of their high magnitude. Some of the consequences of the simple inductive effect have already been mentioned.

The effect reaches a maximum in the trinitromethyl group, which has a Hammett substituent constant $\sigma_{para} = 0.82$, and a Taft polar substituent constant $\sigma^* = 4.54$; these values are the largest that have been recorded for an electrically uncharged group.²⁶ The nitro group itself has the values $\sigma_{para} = 0.78$ and $\sigma_{meta} = 0.71$; the special constant σ^- for reactions involving unshared electron pairs on an atom next to the benzene ring (e.g., the ionization of phenols) is 1.27 for the *p*-nitro group, however. The large difference between σ^-_{para} and σ_{para} reflects the conjugative interaction of the nitro group with *para* substituents. The consequences of these effects may be seen in the acidity of the nitrophenols (*p*-nitrophenol, $K_a = 6.9 \times 10^{-8}$; 2,4-dinitrophenol, $K_a = 1 \times 10^{-4}$; 2,4,6-trinitrophenol (picric acid), $K_a = 0.64$)¹⁰ compared to that of phenol ($K_a = 1.1 \times 10^{-10}$), and in the basicity of the nitrodimethylanilines (*p*-nitrodimethylaniline, $pK_a = 0.9$; *m*-nitro-, $pK_a \simeq 3$) compared to that of dimethylaniline ($pK_a = 5.06$). The effect on the acid strength of benzoic acid, where the site of acidity is one atom farther removed and the nature of the group does not lend itself to effective conjugation, is less pronounced (benzoic acid, $K_a = 6.6 \times 10^{-5}$; *p*-nitro-, $K_a = 4.0 \times 10^{-4}$; *m*-nitro-, $K_a = 3.45 \times 10^{-4}$). The nitro group is, of course, strongly deactivating and *meta* directing toward electrophilic substitution on the benzene ring; the consequences of its activating effect toward nucleophilic substitution are taken up in the section on Reactions.

Nitrolic acids are colorless to pale-yellow solids, such as formonitrolic acid, mp 68° dec., acetonitrolic acid, mp 88° dec., and are easily soluble in water when small.²⁷ They all decompose on moderate heating and slowly on storage. Several benzonitrolic acids have been obtained in two distinct forms, which are in turn distinct from the tautomeric α -nitro- α -nitrosotoluene forms or their dimers. The infrared spectra are grossly similar, but show such differences as to suggest very strongly that the forms are geometric isomers.²⁸ The *syn*-nitro structure has been assigned



(geometrically isomeric benzonitrolic acids)

to the forms with lower acid strength, in consideration of the probability of chelate hydrogen bonding; in the case of the *p*-chloro derivatives, the acid strengths are pK_a 7.7 (*syn*) and 6.1 (*anti*). The *syn* forms form orange-red salts reversibly with base; the *anti* forms react rapidly and

irreversibly to form insoluble, high-melting products.²⁹ Although purely aliphatic examples, such as acetonitrolic acid, have not been obtained in geometrically isomeric forms, they have been observed to give two series of salts, one red and one colorless, attributed to geometric isomerism.³⁰ The red salts are converted to the colorless ones on heating or exposure to light; only the red salts regenerate the original nitrolic acid on acidification, but both give the same ultimate hydrolysis products (acetic acid, hydroxylamine, and nitrous acid).

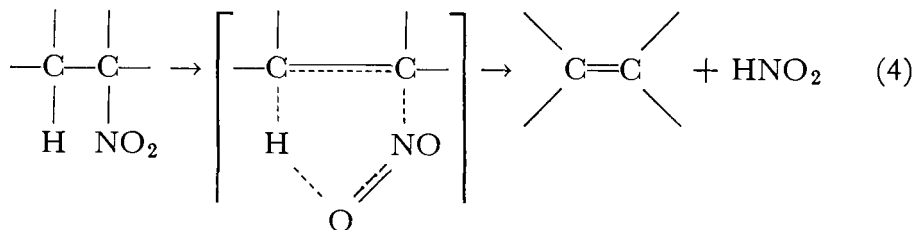
Nitrazones have been touched on in Chapter 11, where they were considered to be α -nitro azo compounds (or the tautomeric nitronic acids), $RN=N-CH(R)NO_2$; they may also be considered as representatives of the C-nitro hydrazone structure, $R-NHN=CRNO_2$ (see pp. 280–281).

All polynitro compounds are potentially explosive; although they are in many instances relatively insensitive and safe to work with, they should always be handled with care and respect for their shattering potentialities. Mononitro compounds are not usually explosive unless they are small and thus close to zero oxygen balance.^{2a, 31} Nitromethane, for example, can be detonated, although it is normally safe to handle. Nitronate salts are in general explosive and should be considered dangerous.

Nitroalkanes appear to have only a low toxicity,³² but aromatic nitro compounds are moderately toxic, especially under conditions of chronic exposure, as may be encountered in chemical manufacture. Prolonged contact with the skin, breathing of the vapors, and ingestion should obviously be avoided.

REACTIONS 1, 2, 32, 33

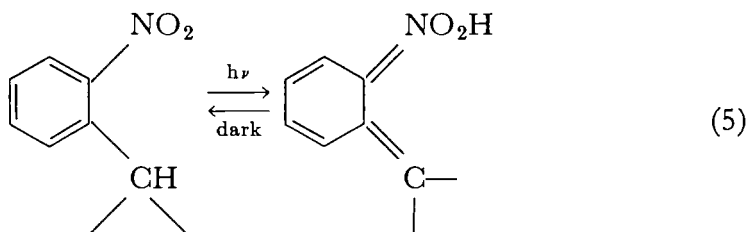
HEAT AND LIGHT Nitroalkanes are decomposed by moderate heating ($> 300^\circ$) with elimination of nitrous acid, forming olefins (Eq. 4).



The process obeys first-order kinetics³⁴ and apparently takes place through a cyclic transition state, resulting in *cis* elimination.^{35a} The reaction is not a clean one, however, and a competing reaction with a higher activation energy, involving homolytic cleavage of the C—N bond, becomes increasingly important at higher temperatures³⁴; fragmentation products are thus formed. Intramolecular oxygen transfer, sometimes

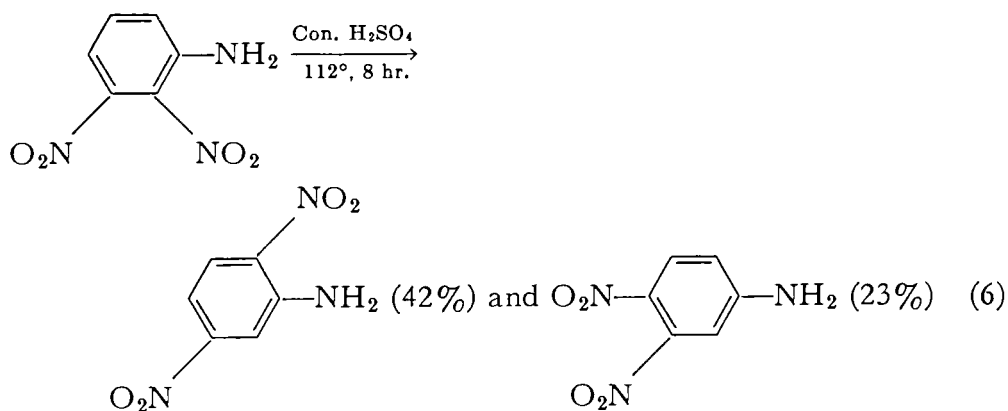
brought about by heat or light, is discussed further on in connection with reduction in general. Aromatic nitro compounds generate free radicals, apparently by either electron or hydrogen transfer, when strongly heated.^{35b}

The absorption of light by the nitro group leads to an excited state that manifests distinctive reactivity in various ways, most of which are taken up in this chapter in connection with the other reagent involved. An example of a purely intramolecular reaction, however, is seen in the photo-induced tautomerization of *o*-nitro alkylbenzenes to nitronic acids³⁶ (Eq. 5); the products are intense blue and return to the starting material



with fading of the color according to first-order kinetics.

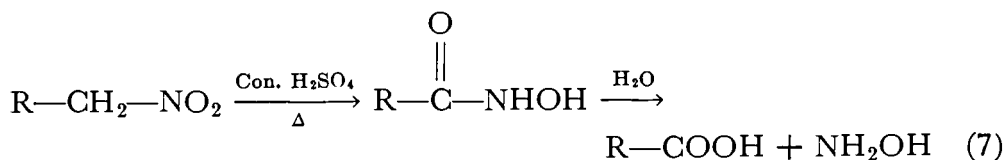
ACIDS Strong acids have no general effect on aromatic nitro compounds, although some examples have been reported of migration of nitro groups under the influence of concentrated or fuming sulfuric acid.³⁷ 2,3-Dinitroaniline, for example, is converted to a mixture of the 2,5- and 3,4-isomers (Eq. 6). These products are themselves unaltered by



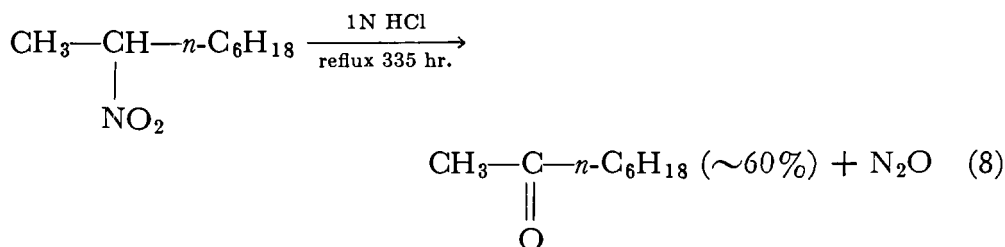
similar treatment. Rearrangement is apparently intermolecular and involves the unusual occurrence of a reversible denitration-nitration sequence.

In contrast to aromatic nitro compounds, aliphatic ones are hydrolyzed by heating with strong mineral acids. The reactions are actually more than simple hydrolysis and require the presence of a hydrogen on the α -carbon, which becomes oxidized to a carboxyl or carbonyl group;

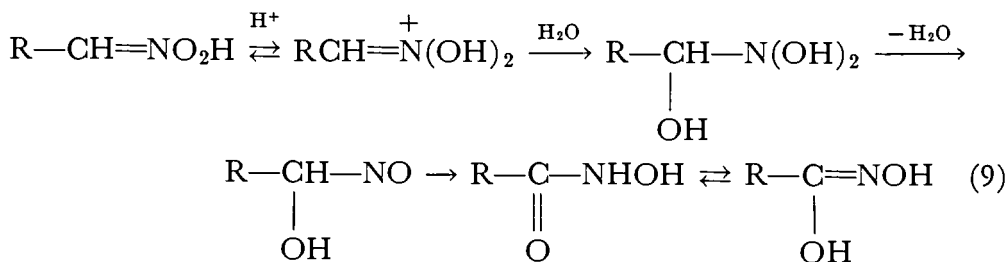
primary nitroalkanes are first converted to hydroxamic acids, which can be isolated if the availability of water for hydrolysis is restricted ³⁸ (Eq. 7).



This reaction is of economic importance as a source of hydroxylamine.³² 1,1-Dinitro compounds behave analogously, but 2,2-dinitro and 1,1,1-trinitro compounds, having no α -hydrogen, are inert.³⁷ Secondary nitroalkanes are in general resistant to hydrolysis, although if sufficient time is given, conversion to ketones may be good.³⁹ The nitro group appears as nitrous oxide, apparently derived from nitroxyl via hypoxynitrous acid (Eq. 8). These reactions are actually those of the isomeric

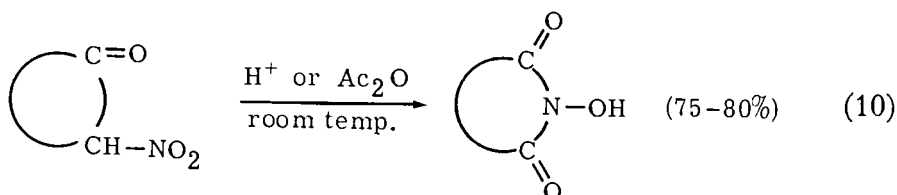


nitronic acids, which are presumably formed by a slow proton removal from the α -carbon of the conjugate acids, $\text{RCH}_2\text{NO}_2\text{H}^+$ or $\text{R}_2\text{CHNO}_2\text{H}^+$. Indeed, it has been shown in one case that treatment of preformed nitronic acid with mineral acid results in particularly easy hydrolysis.⁴ The kinetics of hydrolysis of nitroethane have been studied in 1N hydrochloric acid ⁴⁰; the rate is first order in nitroethane and is identical with the rate of bromination under the same conditions, a reaction whose rate is known to depend on formation of the nitronic acid tautomer. Presumably hydrolysis takes place by attack of water on the unsaturated carbon of a conjugate acid of the nitronic acid bearing the added proton on oxygen (Eq. 9).



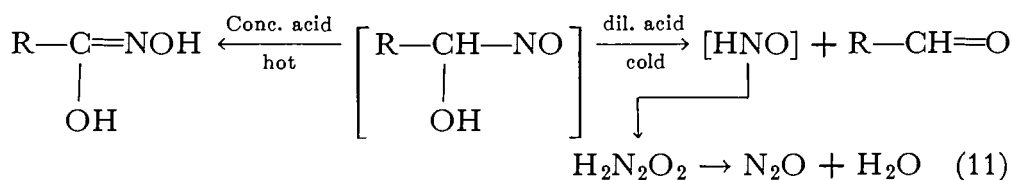
Certain α -nitrocycloalkanones have been observed to undergo a different reaction, involving ring enlargement and retention of the nitrogen,

when treated with strong acid or acetic anhydride ⁴¹⁻⁴² (Eq. 10). This



reaction may be a nitronic acid analog of the Beckman rearrangement of oximes, or may perhaps proceed via ring cleavage and reclosure.

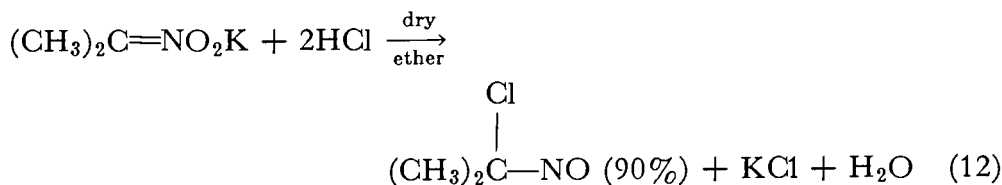
NITRONATE SALTS AND ACIDS Whereas careful acidification of solutions of nitronate salts by adding weak acid to them simply liberates the free nitro compounds or nitronic acids,⁴³ addition of the salt to an excess of strong mineral acid usually brings about the Nef reaction¹¹—formation of nitrous oxide and aldehydes from primary nitroalkanes, or ketones from secondary nitroalkanes. Yields are still seldom more than moderate; heating is not required, and reaction commonly takes place smoothly even at 0°. The Nef reaction presumably begins in the same way as direct acid-catalyzed hydrolysis, by attack of water at the α -carbon of the nitronic acid or its protonated derivative^{44, 45} (Eq. 9). The subsequent difference in behavior of primary nitroalkanes may be attributed to the relative stabilities of the presumed intermediate α -hydroxy nitroso compound under the respective conditions. In hot concentrated acid, its tautomerization to a 1-hydroxy aldoxime (one of the tautomers of a hydroxamic acid) would be a rapid process (cf. Chapter 13), but in cold dilute acid the nitroso structure would have a much longer life, with the result that the course of the reaction could be diverted to formation of an aldehyde by elimination of nitroxyl (Eq. 11). Indeed, transient but



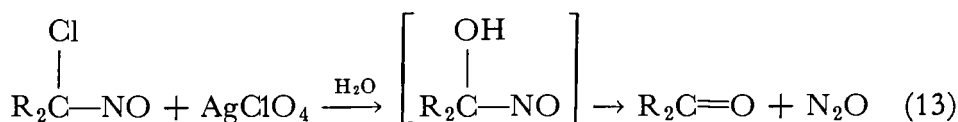
pronounced blue or green colors, characteristic of nitroso compounds, are invariably encountered in Nef reactions. Furthermore, under some circumstances, salts of primary nitroalkanes may give mixtures of aldehyde and hydroxamic acid under the conditions of the Nef reaction.

The kinetics of the Nef reaction, which show first-order dependence on nitronic acid and hydrogen ion concentrations, are consistent with solvent attack on the conjugate acid, $\text{R}_2\text{C}=\text{NO}_2\text{H}_2^+$, as the rate-determining step.⁴⁵ Further support of this view is found in the facts that α -chloro nitroso compounds are formed when dry hydrogen chloride is

used to bring about the reaction ^{35, 46, 47} (Eq. 12), and even in water solution, chloride can sometimes compete noticeably in attacking the proton-

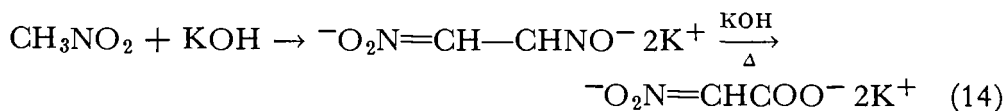


ated nitronic acid. With primary nitroalkanes, the chloronitroso compounds are more or less rapidly tautomerized to hydroximoyl chlorides.⁴⁶ Treatment of α -chloro nitroso compounds with silver perchlorate in aqueous-alcoholic solution gives the ordinary Nef products (Eq. 13), thus further confirming the view that α -hydroxy nitroso compounds are



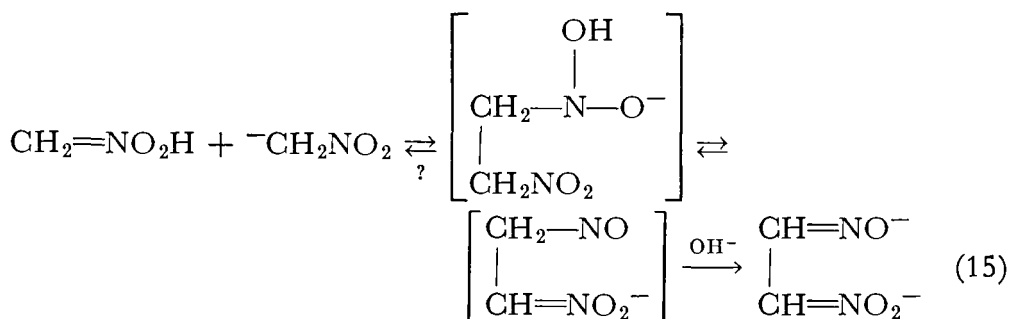
intermediates.⁴⁸ Nef reactions are often accompanied by the formation of nitrolic acids or pseudonitroles as by-products. These apparently arise as a result of autoxidation of some nitronate salt, releasing nitrite ion, which nitrosates the nitronic acid upon acidification (cf. the discussion of oxidation, ahead).

BASES Salt formation is, of course, the initial reaction taking place between all bases and primary or secondary nitroalkanes. Although such salts are quite stable enough to be isolated, they are reactive substances and frequently undergo further reaction, especially when heated or allowed to stand in solution; nitronic acids and their salts bearing aryl or electron-withdrawing groups such as carboethoxy are more stable, however.⁴³ The alkali salts of nitromethane are relatively unstable, being fairly quickly converted to salts of methazonic acid (nitroacetaldoxime)⁴⁹ (Eq. 14), which in turn easily undergo conversion to nitroacetate salts.



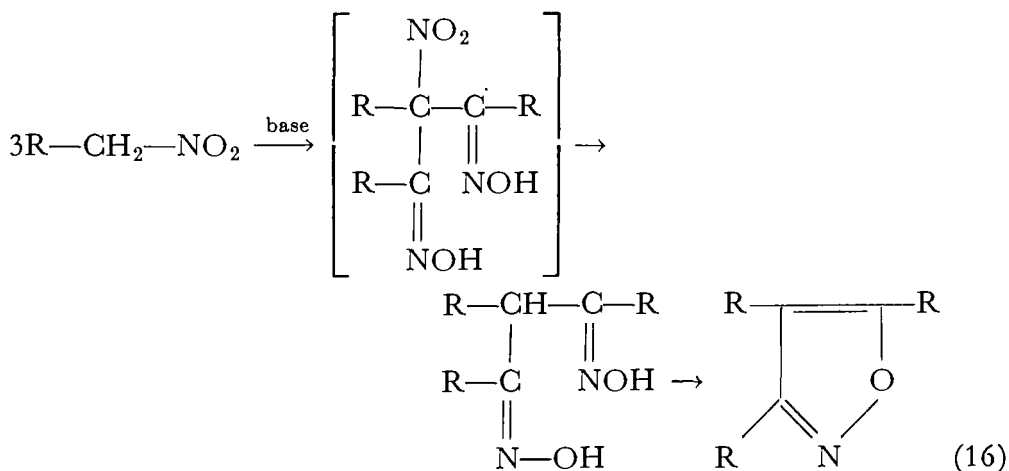
This series of reactions constitutes in fact a practical preparative route to nitroacetic acid. Kinetic studies of the reaction, which is subject to a positive primary salt effect, indicate the rate-determining step involves the reaction of two negatively charged species.⁵⁰ This step may be C—C bond formation between two methylenenitronate anions, or may be conversion of β -nitrosoethylidenenitronate anion to methazonate dianion

induced by hydroxide ion (Eq. 15). The latter possibility implies that



C—C bond formation occurs by an analog of the Nef reaction, in which a nitronate anion plays the role of the attacking nucleophile as a carbanion, adding to a molecule of un-ionized nitronic acid. The observed kinetics would require that the steps leading up to the rate-determining one be reversible, of course. A chain reaction involving nitromethyl radicals cannot be ruled out as a possibility. Either path would account for the reported condensation of a secondary nitrosoalkane (3-nitrosocamphor) to a β -nitroso nitro compound,⁵¹ there being in this instance insufficient α -hydrogens for the further progress of reaction.

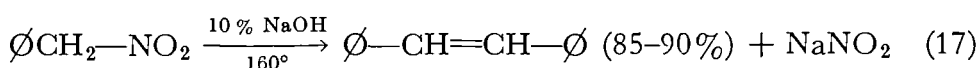
Primary nitroalkanes are also condensed by alkali; the product usually isolated is an isoxazole arising from three molecules of nitroalkane, accompanied by some nitrile. The way in which this condensation takes place is partially illuminated by the fact that an intermediate, a 1,3-dioxime, can be isolated when an amine is used as a catalyst in place of alkali⁵² (Eq. 16). The path of this reaction is probably analogous to



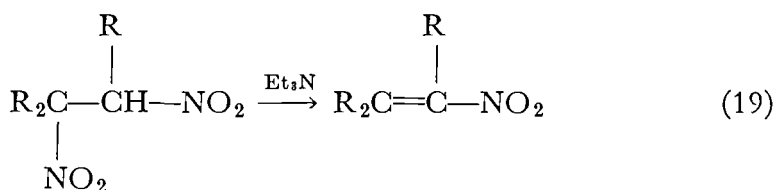
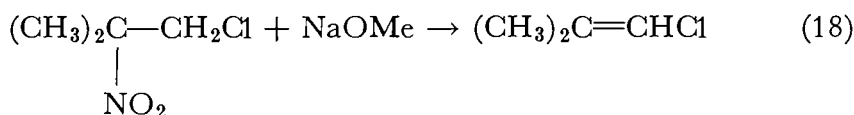
that of methazonate formation, with the difference that the anion of the initial dimeric adduct attacks a third molecule of nitronic acid, giving a 2-nitro-1,3-dioxime. The remaining nitro group is apparently replaced

by hydrogen and becomes a nitrate ion, a process for which there is ample precedent among nitro compounds bearing electron-withdrawing α -substituents (e.g., tetranitromethane is hydrolyzed to nitroform and nitrate by alkali).⁵³

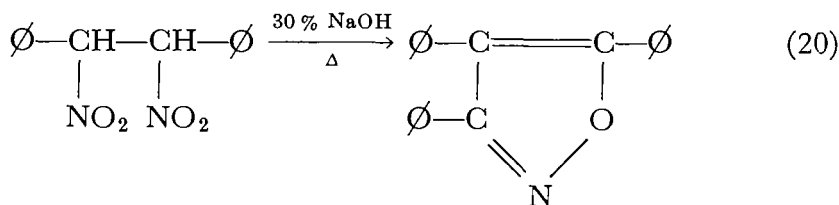
A different type of condensation formally entailing 1,1-elimination of nitrous acid is displayed by α -nitrotoluene, which gives stilbene and sodium nitrite when heated with sodium hydroxide⁴⁴ (Eq. 17); the reaction is not general, and the evidence is insufficient to determine whether a carbene intermediate is involved. 1,2-Elimination of nitrous acid has



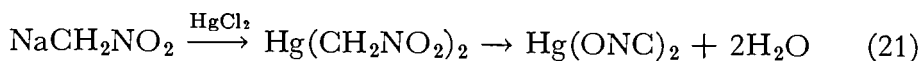
been observed with some tertiary nitroalkanes having a β -hydrogen at least slightly activated by an electron-withdrawing substituent^{55, 56}



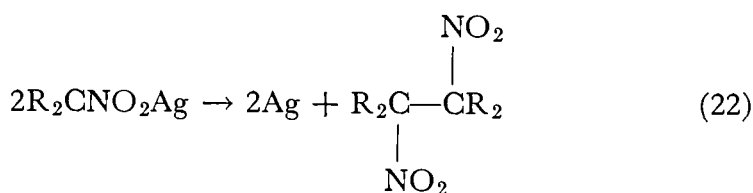
(Eqs. 18, 19), and in one instance with a secondary nitroalkane, *trans*-1,2-dinitrocyclohexane,⁵⁷ although in other instances vicinal dinitroalkanes yield isoxazoles when treated with bases⁵⁸ (perhaps, nevertheless, by a path beginning with 1,2-elimination) (Eq. 20).



Heavy-metal salts of nitroalkanes behave somewhat differently from other salts. Mercuric methylenenitronate, for example, easily loses water to form mercuric fulminate⁵⁹ (Eq. 21). Silver nitronates undergo



spontaneous internal electron transfer, forming metallic silver and a dimer of the anion⁵⁸ (Eq. 22).



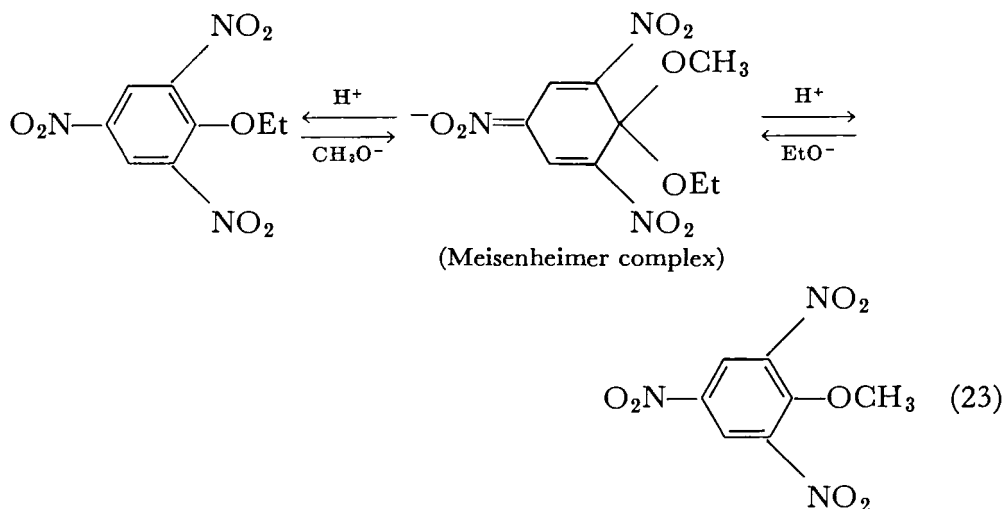
Aromatic nitro compounds react with most bases by addition of one sort or another, in some circumstances culminating in nucleophilic displacement. The simplest form of addition manifests itself in the formation of more or less loose complexes, such as the blood-red oil formed from aniline and nitrobenzene, whose components cannot be separated by distillation, but which are instantly broken apart by dilute mineral acid. The intensity of the interaction increases with accumulation of nitro groups, and 1,3,5-trinitrobenzene and its derivatives, such as picryl chloride, will even form reasonably stable complexes with the more electron-rich aromatic hydrocarbons, such as naphthalene. Such products are of practical importance in purification and identification and have been widely studied. Complexes of this type are called charge-transfer or donor-acceptor complexes, terms arising from the fact that they have a low-energy transition from a relatively nonpolar ground state to an excited state in which an electron has been transferred from the donor to the acceptor ^{60, 62}: $\text{AD} + h\nu \rightarrow \text{A}^-\text{D}^+$. The energy of these transitions corresponds to absorption in the near ultraviolet or visible range and hence generally gives rise to intense color. The wavelengths of these characteristic charge-transfer absorption bands for complexes of a given acceptor are in roughly linear relation to the ionization potential of the donor molecule. The formation of charge-transfer complexes is not restricted to nitro compounds, and the most familiar example, quinhydrone, contains no nitrogen whatever.

When amines react with trinitrobenzene and derivatives, interaction is of course very strong and may even approach complete electron transfer in the ground state.⁶³ TNB and TNT form 1:2 adducts with diethylamine; the reaction is reversible, rapid, and kinetically third order.⁶⁴ Tetranitromethane also forms addition complexes with olefins and electron-rich aromatic compounds.²

The adduct of *p*-iodoaniline and *sym*-trinitrobenzene, a red crystalline solid, has been examined by X-ray crystallography.⁶⁵ The rings of the two components approach each other face-to-face, but the interplanar and intergroup distances remain greater than 3 Å; the complexes of hydrocarbons, such as hexamethylbenzene, are apparently arranged similarly. It is clear that at such distances, the components are not held together by ordinary valence bonds; nevertheless, charge-transfer complexes have appreciable dipole moments, part of which must result from

induced polarization of the donor by the acceptor, a form of weak interaction between the respective π -electron systems.⁶⁰⁻⁶²

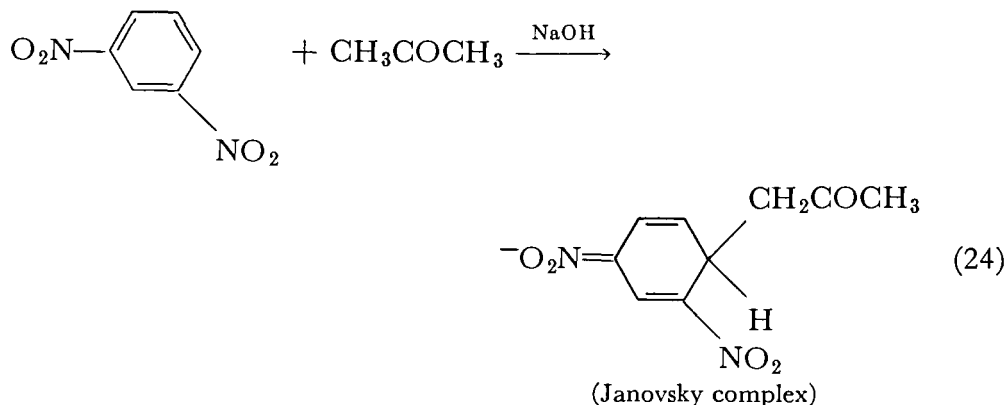
Stronger bases, particularly alkalis and alkoxides, attack positions *ortho* or *para* to nitro groups and form new anions, termed "Meisenheimer complexes," in which the components are held together by a normal sigma bond^{66, 67}; acidification usually reverses their formation. These complexes are usually intensely colored (e.g., blue in the case of 2,4-dinitroanisole). Their nature has been amply demonstrated by both chemical and spectroscopic means,⁶⁸ as illustrated by the example of the picryl ethers. Equivalence of the resident and added alkoxyl group can be demonstrated by preparing the complex from methyl picrate (trinitroanisole) and sodium ethoxide and from ethyl picrate and sodium methoxide; the products are identical (Eq. 23). Equivalence has also been



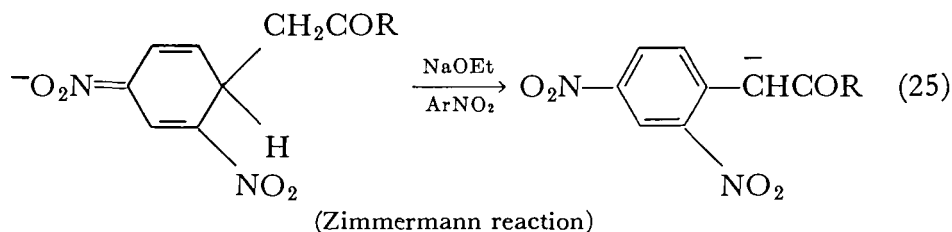
demonstrated by isotopic labeling; when methyl picrate is converted to the potassium salt of its complex with methoxide ion enriched with O^{18} and then regenerated by acidification, approximately half of the excess isotope is then found in the recovered methyl picrate.⁶⁹ The Meisenheimer complexes are thus stable, isolable intermediates in nucleophilic displacement on an activated aromatic ring.⁶⁷

When the treatment of a *m*-dinitro- or 1,3,5-trinitrobenzene derivative with alkali is carried out in the presence of a ketone bearing an α -methylene group, the color of the complex formed is distinctly different (e.g., purple from *m*-dinitrobenzene), and has been used as means for the qualitative detection of such structures. These complexes incorporate a molecule of the ketone (more properly, the anion derived from it) and are usually termed "Janovsky complexes."^{66, 68} The structure of the Janovsky complexes was in doubt for many decades following their discovery, the principal point of uncertainty being whether the ketone was

joined through carbon or oxygen. Spectroscopic and other evidence now appears decisive in favor of carbon attachment (Eq. 24).⁷⁰ Under the more strongly basic conditions of alcoholic sodium ethoxide, the



same reagents form yet a different type of complex, whose color is red when derived from *m*-dinitro compounds; this is known as the Zimmermann reaction.^{54, 66} The colors result from oxidation of the Janovsky complexes through successive proton removal and electron transfer to another molecule of nitro compound (Eq. 25). Neither the Janovsky nor the Zimmermann reactions has so far been found to be of preparative

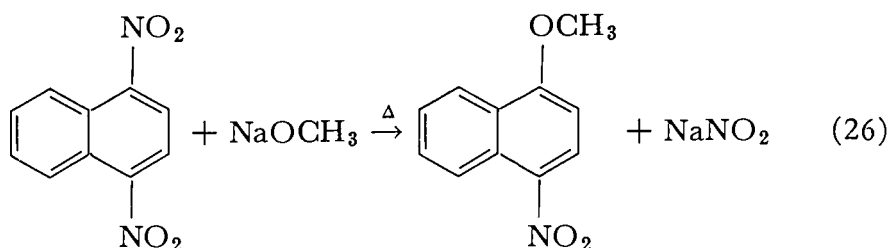


utility, although they have diagnostic value.

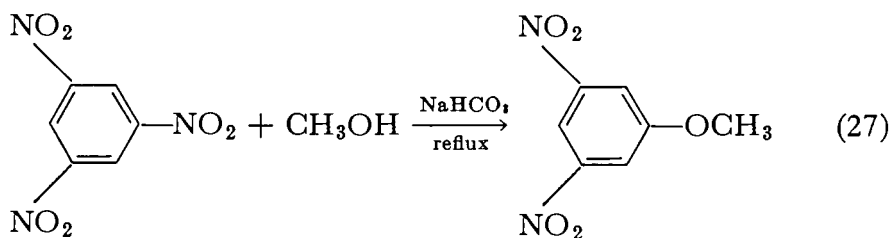
Nucleophilic substitution on aromatic nitro compounds⁷¹ is not only promoted by accumulation of nitro groups, but also by the presence of a good leaving group *ortho* or *para* to a nitro group. The increase of reactivity of the chlorine in the stepwise transition from virtually unreactive chlorobenzene to picryl chloride (2,4,6-trinitrochlorobenzene), which approaches acyl chlorides in reactivity, is a well-known example of a phenomenon general to electron-withdrawing substituents and needs no amplification here other than to point out that halogen *ortho* or *para* to nitro groups is replaceable not only by alkali, but also by such weaker bases as amines and hydrazines. It is less well known, however, that activation by a nitro group can be far more intense in the *ortho* position than in the *para*⁷¹; *o*-nitrochlorobenzene, for example, reacts with piperidine 2 to 60 times as fast (depending on the solvent) as does the *para*

isomer.⁷² The ratio of reactivity between *ortho* and *para* attack is markedly influenced by both solvent and nucleophilic reagent, however, and may be reversed under some circumstances.⁷¹

A nitro group itself can function as a leaving group, departing as nitrite ion, hence *p*-dinitro compounds are susceptible to solvolysis of one nitro group. The reaction of 1,4-dinitronaphthalene with sodium methoxide (Eq. 26) is a good example of such a reaction; it is kinetically

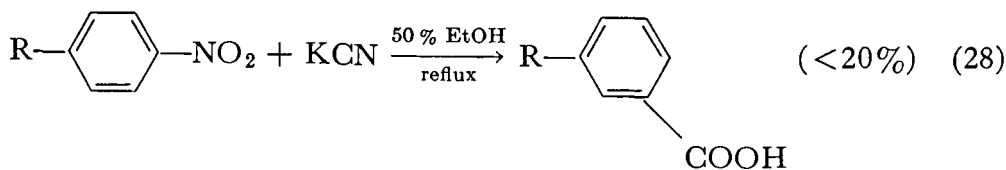


second order, and the activation energy is 19.2 kcal/mole.⁷³ The activating effect of one nitro group on another toward nucleophilic displacement also extends to groups *meta* to each other, but the effect is weaker and has been observed only with 1,3,5-trinitrobenzenes. TNB, for example, is converted to 3,5-dinitroanisole by refluxing with sodium bicarbonate in methanol⁷⁴ (Eq. 27). It has been suggested that this

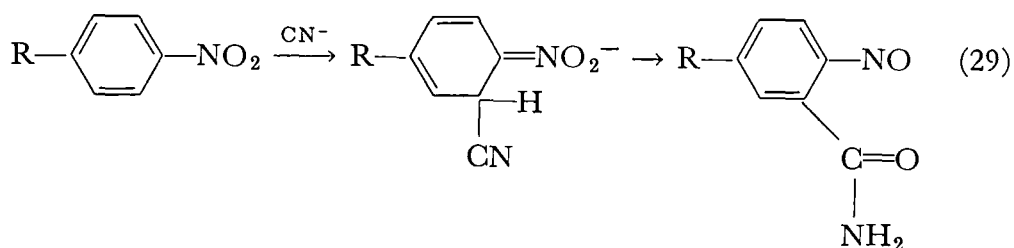


may not be the simple nucleophilic displacement that it appears, however, and may involve initial attack at an unsubstituted position.

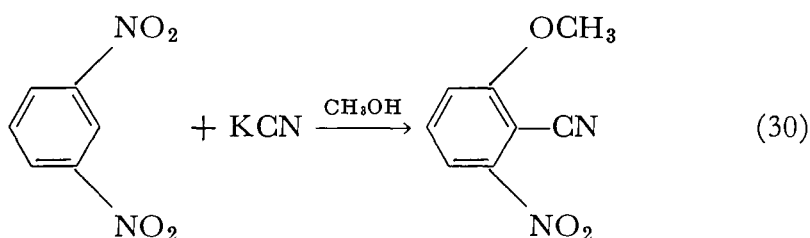
There is, indeed, a class of reaction in which hydrogen on a nitrobenzene ring is substituted by a nucleophile. The best-known example is the von Richter reaction, in which a nitrobenzene is heated with aqueous alcohol containing an alkali cyanide⁷⁵; the net result is the substitution of a carboxyl group *ortho* to the position originally occupied by the nitro group, which itself is replaced by hydrogen (Eq. 28). This



reaction is believed to proceed through attack by cyanide ion at an *ortho* position, followed by isomerization to an *o*-nitrosobenzamide (Eq. 29).

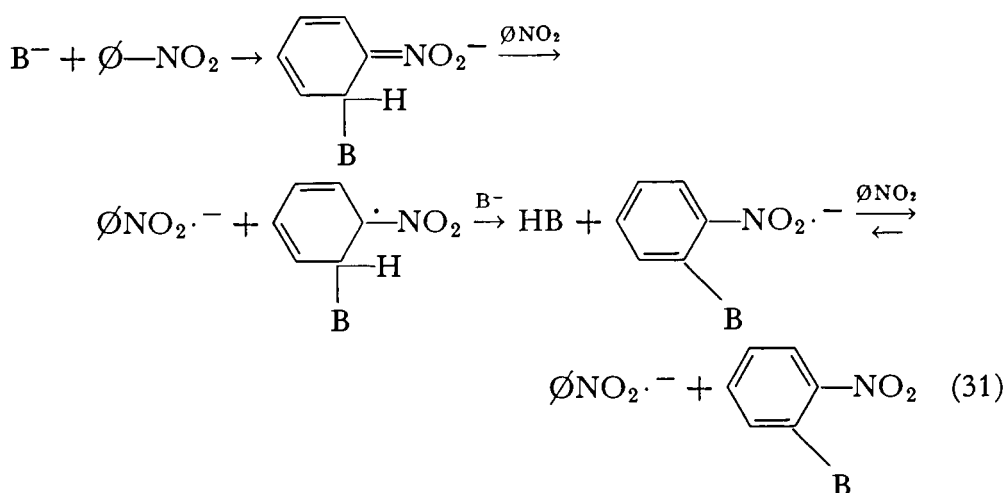


Such compounds have indeed been shown to yield benzoic acids with loss of the nitroso and amino groups as nitrogen ⁷⁶ (cf. Chapter 13), and it has been shown by isotope-labeling experiments that oxygen is transferred from the nitro group directly to the cyano carbon.⁷⁷ When there are two nitro groups *meta* to each other, the reaction takes a different course; the ejected nitro group is replaced by alkoxyl instead of hydrogen and the product is a nitrile ⁷⁸ (Eq. 30). It is significant that substitution takes place at the vicinal position, notwithstanding steric hindrance, illustrating

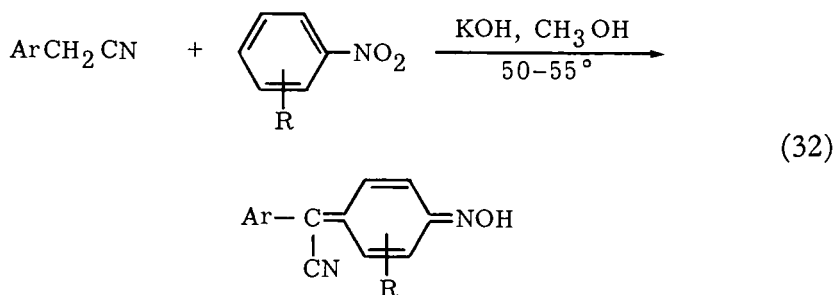


again the greater activating effect *ortho* to nitro groups. This type of reaction has been realized with only one nitro group present, with 6-nitroquinoline.⁷⁹

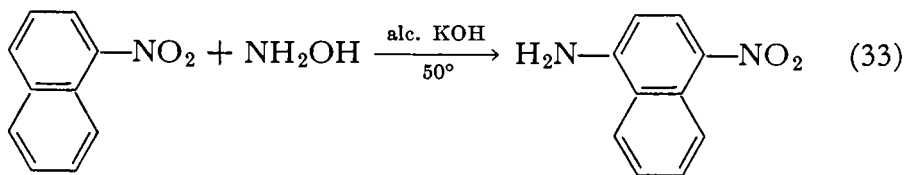
Nucleophilic substitution of hydrogen of nitrobenzenes can also be accomplished with other reagents,⁸⁰ such as alkalis. Yields up to 50% of *o*-nitrophenol are obtained when nitrobenzene is heated at 60–70° with powdered potassium hydroxide, for example.^{71b} Although this reaction can be written as a purely ionic process, there is good reason to believe that neutral free radicals and anion radicals are involved after the initial attack ⁵⁴ (Eq. 31); a clear electron-spin-resonance signal of the nitrobenzene anion radical, $\text{C}_6\text{H}_5\text{NO}_2\cdot^-$, is given by alkaline solutions of nitrobenzene. The anion radicals eventually disproportionate and thus give rise to various reduction products of the nitro compounds, not infrequently in the form of tarry mixtures. In the case of nucleophilic attack by the carbanion of phenylacetonitrile, however, the reactions are unusually



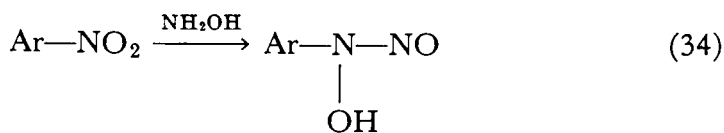
clean, and high yields of quinomethane oxime derivatives can be obtained⁸¹ (Eq. 32). When the attacking nucleophile itself bears an



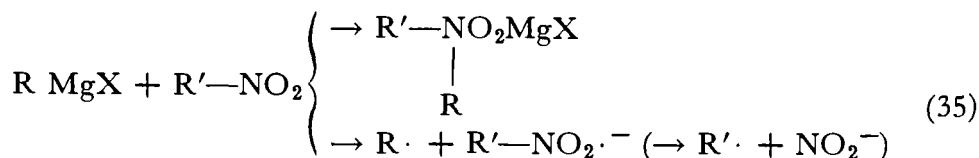
ejectable fragment, as hydroxylamine does, substitution is less complicated by redox reactions; indeed, suitably activated aromatic nuclei can be aminated readily in this way⁸² (Eq. 33). In some instances, intermediates corresponding to the addition of the sodium derivative of hydroxylamine to the nitro compound precipitate. Condensation of hydroxylamine with the nitro group itself to form an N-nitrosohydroxylamine (Eq. 34) may



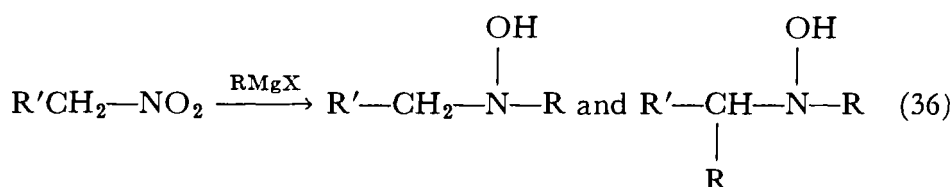
be an important competing reaction.⁸³



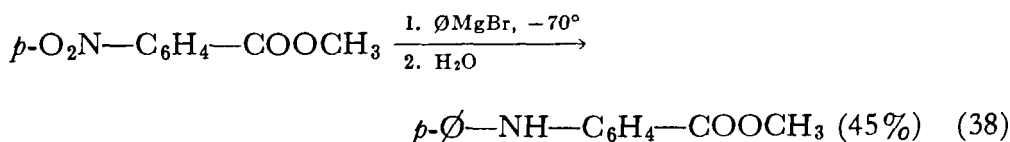
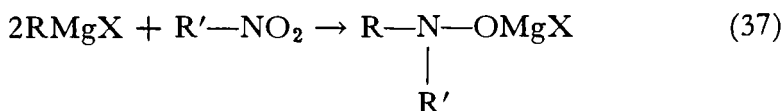
ORGANOMETALLIC REAGENTS Nitro compounds react in at least four ways with organometallic reagents,^{84a} although in a given instance all of the possibilities are not necessarily important. They are: (1) addition to nitrogen to give dialkylnitronate salts (Eq. 35); (2) addition to oxygen and separation of RO^- , leaving $\text{R}'\text{—NO}$; (3) electron transfer to form a nitro anion radical (Eq. 35); and (4) addition to the α -carbon, leading



eventually to hydroxylamines^{32, 84b} (Eq. 36). The first three possi-



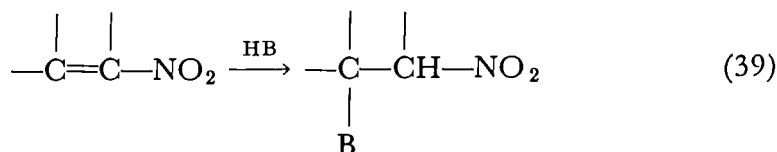
bilities are commonly observed with nitro compounds having no α -hydrogen. When only one equivalent of organometallic compound is taken, the dialkylnitronates are generally formed in good yields^{9a, 85}; acidification of them does not release isolable dialkylnitronic acids, but instead gives rise to dialkyl nitroxides, $\text{R}_2\text{NO}\cdot$, in low (1 to 30%) but preparatively significant yields.^{84a} With more than one equivalent of reagent, oxygen removal may take place, usually to give hydroxylamines^{84–86} (Eq. 37), but sometimes to give secondary amines^{87a} (Eq. 38). With primary nitro



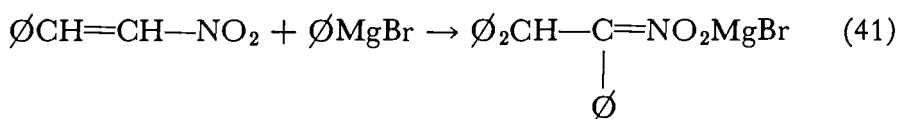
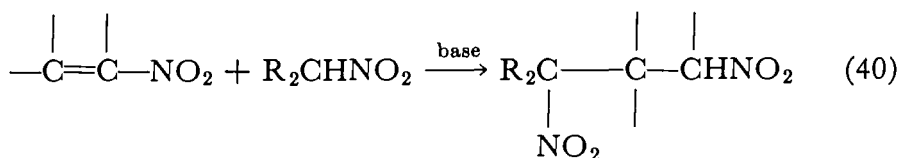
compounds, simple salt formation may be the only reaction unless more than one equivalent of Grignard reagent is used.⁸⁶ Trinitrobenzene reacts as a nitro olefin and undergoes conjugate addition to give a salt of a 1,3,5-trialkyl-2,4,6-trinitrocyclohexane.^{87b}

NITRO OLEFINS AND NUCLEOPHILES Nitro olefins react with most nucleophiles in a distinctive manner, giving rise to products resulting

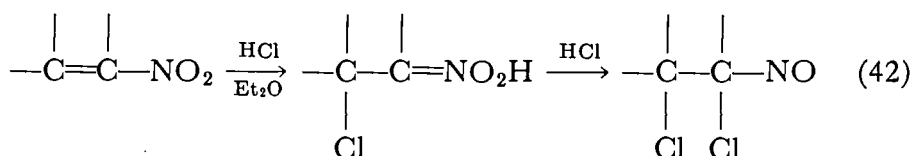
from 1,4-addition analogous to the Michael reaction. Alcohols, mercaptans, and amines, *inter aliae*, add readily⁸⁸ (Eq. 39); nitroethylene is thus a nitroethylating agent analogous to acrylonitrile as a cyanoethylating agent. The addition is in some instances, notably with ω -nitrostyrenes,



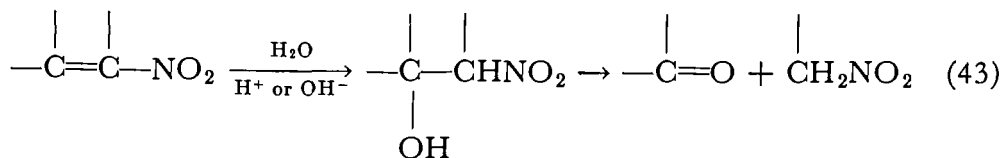
easily reversed.⁸⁹ Nitronate salts can serve as an addend, giving rise to dinitroalkanes^{88, 90} (Eq. 40). Grignard reagents add analogously, giving nitronate salts^{4, 91} (Eq. 41). Even hydrogen chloride takes part in this



reaction, but in this case the initially formed β -chloronitronic acids react with more reagent to give α, β -dichloronitroso compounds (or the isomeric hydroxamoyl chlorides)⁹² (Eq. 42). Addition of water, which may be

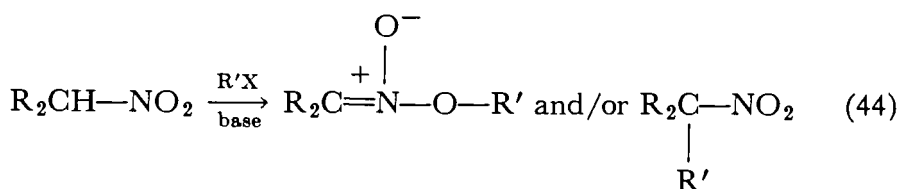


brought about by treatment of nitro.olefins with dilute acids or alkalis, gives β -nitro alcohols, which may undergo a reverse Henry reaction (dealdolization; see ahead) to give an aldehyde or ketone and a smaller nitroalkane (Eq. 43).

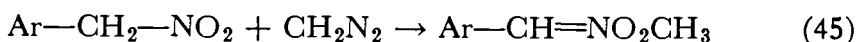


ALKYLATION Alkylation is a reaction confined to aliphatic nitro compounds having an α -hydrogen and may take place on oxygen, giving nitronate esters, or on the α -carbon, giving substituted nitro compounds

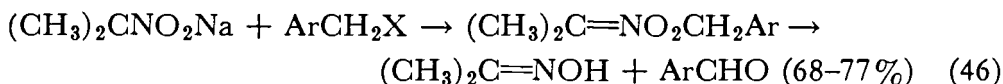
(Eq. 44). Normally a base is required, for the reaction is a nucleophilic



displacement by the nitronate anion. Diazomethane, however, may react slowly without added base to form methyl nitronates⁹³ (Eq. 45); this behavior has been observed only with α -aryl nitroalkanes, not with

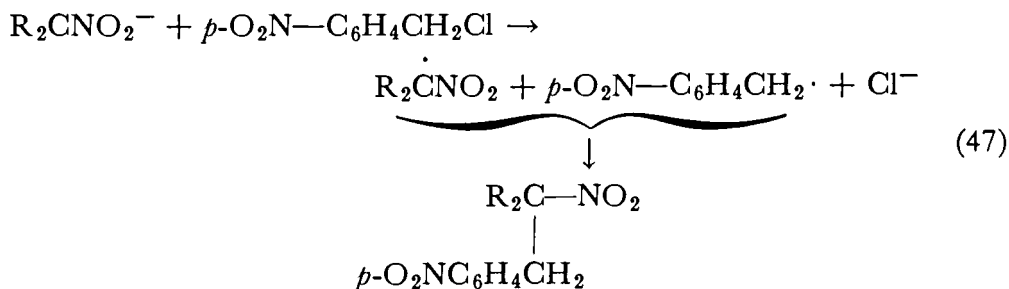


purely aliphatic examples.⁸ Alkylation of salts of simple nitroalkanes generally takes place overwhelmingly on oxygen; the conditions required are such as to cause decomposition of the rather labile nitronate esters, and the products actually isolated are usually an oxime and an aldehyde (or ketone) derived from the alkylating agent. Indeed, this process has been adapted as a useful aldehyde synthesis⁹⁴ (Eq. 46). Only with



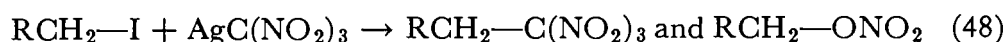
oxonium salts, which are exceptionally active alkylating agents, does alkylation proceed under conditions mild enough to allow the isolation of purely aliphatic alkyl nitronates.⁸

Certain alkylating agents may give appreciable amounts of C-alkylation. α -Halo nitroalkanes constitute an example; C-alkylation is promoted in the order $\text{R}-\text{I} > \text{R}-\text{Br} > \text{R}-\text{Cl}$, but at best the yields are low.⁹⁵ *p*-Nitrobenzyl chloride (but not the iodide) and *p*-nitrobenzyl trimethylammonium chloride behave exceptionally; with them, C-alkylation assumes almost quantitative proportions. It has been proposed that this is the result of a fundamental mechanistic difference, according to which an electron transfer first takes place, giving a pair of free-radicals which then combine⁹⁶ (Eq. 47). In support of this view is the fact that

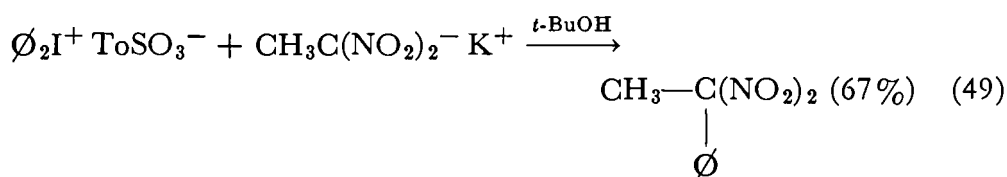


the presence of *p*-dinitrobenzene, an exceptionally good electron acceptor, suppresses C-alkylation drastically, with the result that O-alkylation occurs.

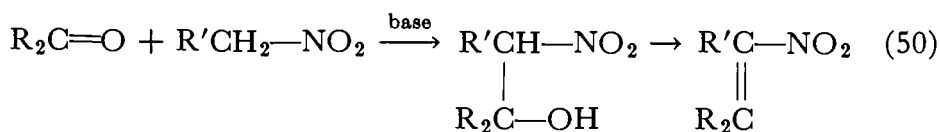
Alkylation with activated olefins by the Michael reaction is successful in a wide spectrum and gives good yields of C-substituted products.⁹⁷ Mannich bases⁹⁸ and methylolamines⁹⁹ also effect C-substitution. C-Alkylation of nitroform through its silver salt has been accomplished in good yield with a variety of primary alkyl iodides.¹⁰⁰ Secondary alkyl iodides attack oxygen primarily and even some primary alkyl iodides, such as *n*-octyl iodide, give more O- than C-alkylation; the product isolated is then an alkyl *nitrate* (Eq. 48), the result of an incompletely understood cleavage reaction.



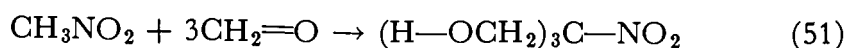
C-Arylation of salts of both mononitroalkanes¹⁰¹ and *gem*-dinitroalkanes¹⁰² has been accomplished in good yields with iodonium salts (Eq. 49).



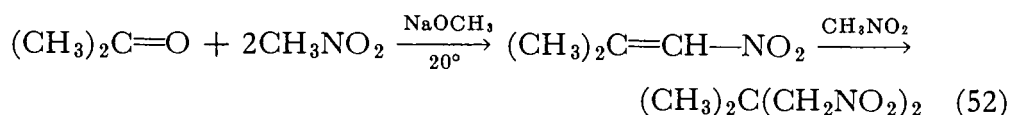
REACTIONS WITH ALDEHYDES AND KETONES Nitroalkanes having an α -hydrogen undergo base-catalyzed addition to the carbonyl group of aldehydes, more difficultly to ketones, to form β -nitro alcohols, or their dehydration products, nitro olefins (Eq. 50). This reaction, which is



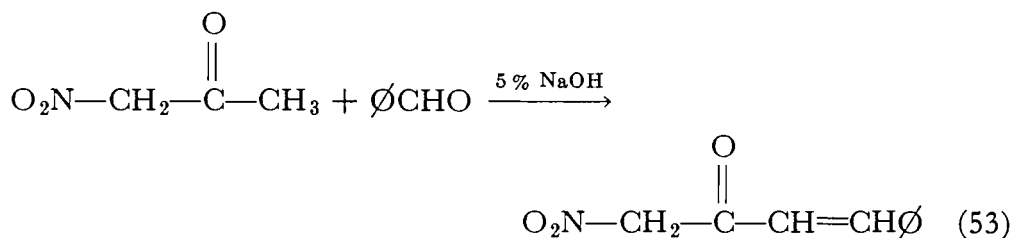
basically an aldol condensation, is known as the Henry reaction.^{103, 104} Olefin formation is more likely to be encountered when benzaldehydes are used and with a weakly basic catalyst (e.g., secondary amine) rather than with strong alkali.¹⁰⁵ There is reason to believe that olefins are sometimes not produced in the primary reaction, but in acidification in the work-up. If there is more than one α -hydrogen, multiple condensation may follow, especially with the more reactive carbonyl compounds, such as formaldehyde (Eq. 51). On the other hand, two molecules of



nitroalkane may condense with one carbonyl group if the circumstances allow the intermediate formation of nitro olefin ¹⁰⁶ (Eq. 52). The Henry

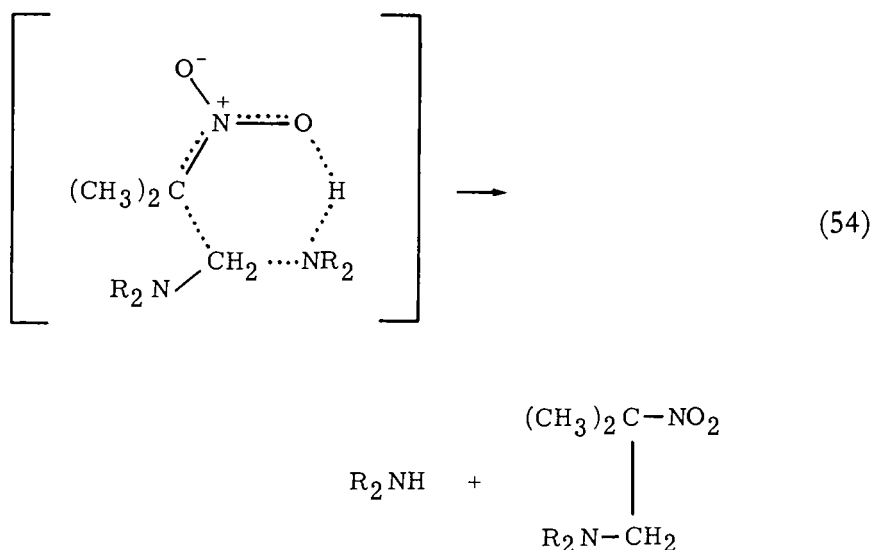


reaction is not a vigorous one, and it is possible to carry out condensation selectively ¹⁰⁷ (Eq. 53).



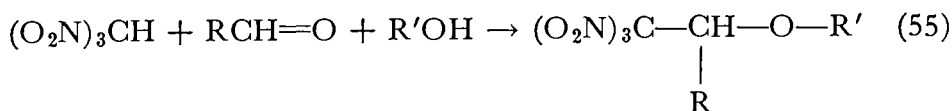
The Henry reaction is reversible; the acidity of certain β -nitro alcohols, originally attributed to the hydroxyl group, has been shown to result from dissociation into aldehyde and nitroalkane. ¹⁰⁸

The Mannich reaction can be realized with nitroalkanes in the conventional way, or with preformed *gem*-diamine ¹⁰⁹ (Eq. 54). In the latter form, the reaction is retarded by base, hence it may be inferred that

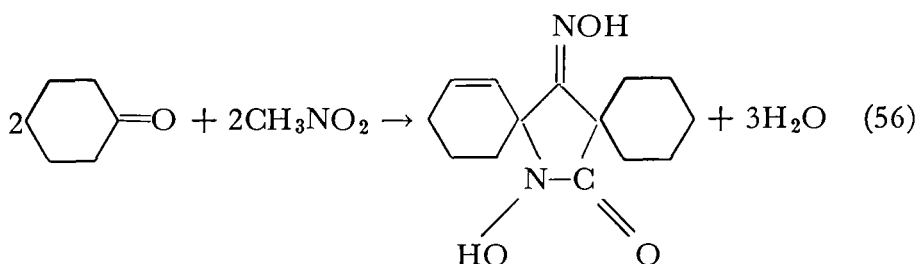


either the free nitronic acid or a protonation product of the *gem*-diamine is involved, and condensation may be a concerted process taking place through a quasi-cyclic transition state. Alkoxymethylation, an analogous

process, can also be realized, as in the case of trinitromethane reacting with aldehydes or acetals in the presence of alcohols¹¹⁰ (Eq. 55).



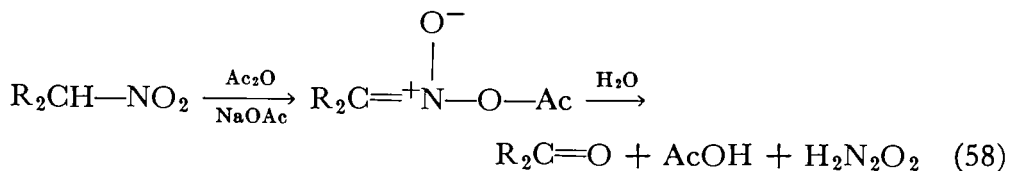
When the Henry reaction is carried out with nitromethane and cycloalkanones, a by-product of double molecular weight accompanies the expected nitro olefins and nitro alcohols. These by-products were eventually recognized after much effort as oximes of cyclic keto hydroxamic acids^{105, 111} (Eq. 56).



ACYLATION Nitroalkanes are reported to be inert toward acetic anhydride alone, but in the presence of bases, such as sodium acetate, primary nitroalkanes undergo an acetolysis version of the Nef reaction. The reported¹¹² products are triacetylhydroxylamine and a carboxylic acid (Eq. 57), but the material balances are very incomplete; the transient formation of intense blue colors suggests that α -acetoxy nitroso compounds

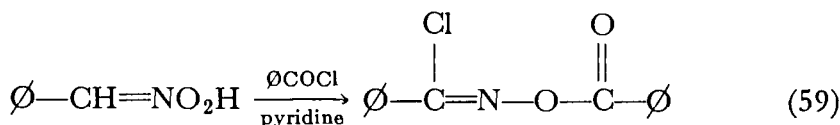


are intermediates. Under similar conditions, secondary nitroalkanes form isolable acetic nitronic anhydrides in low yields (Eq. 58), accompanied by carbon dioxide evolution and other unidentified products.¹¹³

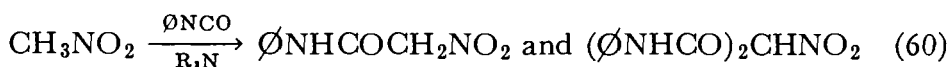


The anhydrides so formed are distillable, but can explode on heating; the evidence for their structure is hydrolysis to ketone, acetic acid, and hyponitrous acid, and solvolysis by aniline to acetanilide. α -Nitrophenylacetone nitrile has been benzoylated through its sodium or silver salt to form what is also apparently a mixed nitronic anhydride.¹¹⁴ Attempts

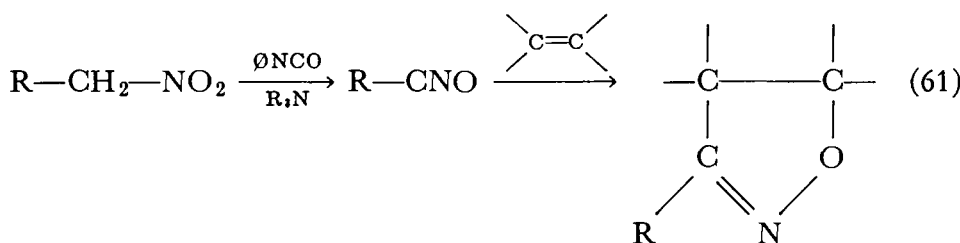
to benzoylate primary nitroalkanes through their nitronic acid tautomers, however, have led only to hydroxamic acid derivatives ¹¹⁵ (Eq. 59).



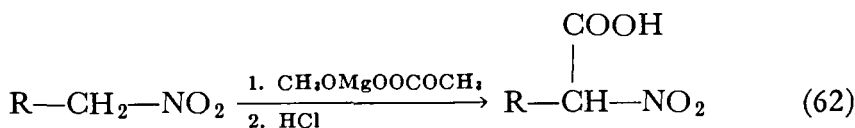
The occurrence of C-acylation, manifested in the formation *o*-nitroacetylbenzoic acid in low yield, has been reported in the reaction of phthalic anhydride with the sodium salt of nitromethane.¹¹⁶ Phenyl isocyanate has also been reported to accomplish C-acylation of nitromethane ¹¹⁷ (Eq. 60), but other primary nitroalkanes instead undergo



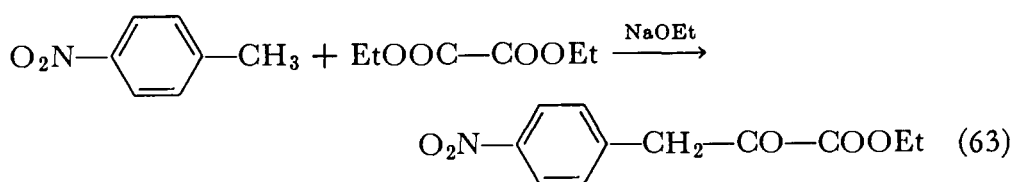
dehydration to nitrile oxides, isolated as their adducts with olefins (Eq. 61). C-Acylation can also be accomplished in good yield through



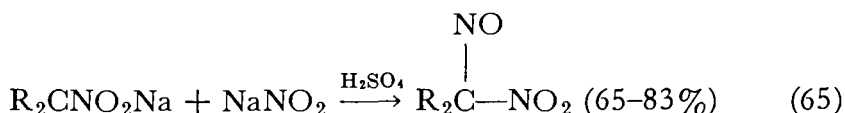
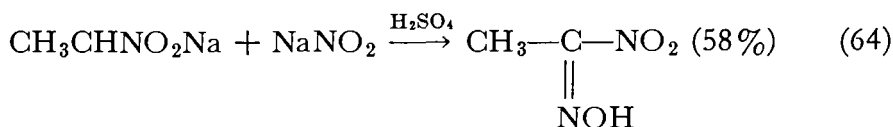
carboxylation with magnesium methylcarbonate, a useful preparative method for α -nitro acids and their esters ¹¹⁸ (Eq. 62).



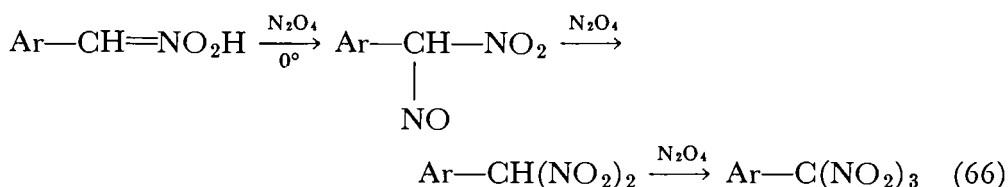
Aromatic nitro compounds are ordinarily inert to acylation, unless an alkyl group is in an *ortho* or *para* position. The activating influence of the nitro group is partially transmitted to the α -hydrogens, which are susceptible to base-catalyzed condensations, such as that with oxalic esters ¹¹⁹ (Eq. 63). The Henry reaction can also be carried out on such substrates.¹²⁰



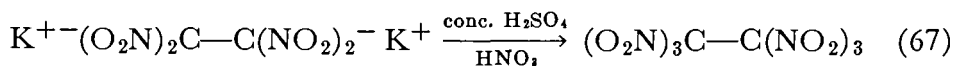
NITROSATION AND NITRATION C-Acylation is the general rule for nitrosating agents, which convert primary nitroalkanes to nitrolic acids⁵ (red alkali salts) and secondary nitroalkanes to pseudonitroles³⁵ (blue), while leaving tertiary nitroalkanes (colorless) untouched (Eqs. 64 and 65). These reactions constitute the "red, white, and blue test" for determining



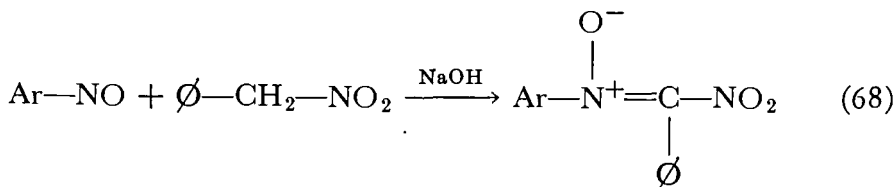
the degree of α -substitution on nitroalkanes. Nitrogen tetroxide also accomplishes nitrosation of nitronic acids and their salts, but excess of the reagent may oxidize the nitroso groups first formed, giving rise to *gem*-dinitro and even 1,1,1-trinitro compounds¹²¹ (Eq. 66). Nitration can



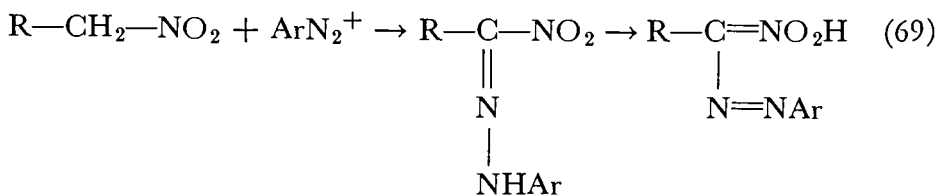
exceptionally be accomplished with "mixed acids"¹²² (Eq. 67).



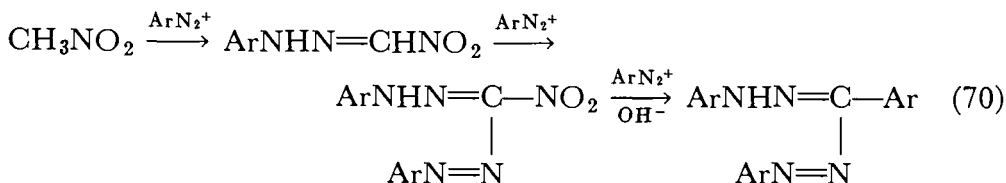
C-Nitroso compounds condense with primary nitroalkanes just as they do with other active methylene compounds, with or without concurrent oxidation, producing anils or nitrones¹²³ (Eq. 68) (cf. Chapter 13).



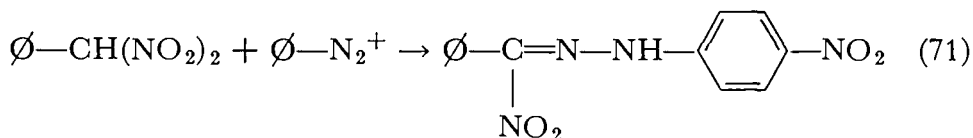
DIAZONIUM COUPLING Primary and secondary nitroalkanes couple with diazonium salts to give nitrazones or the related azo compounds^{124, 125} (Eq. 69). Nitromethane couples with either one, two, or three equiva-



lents of diazonium salt. The usual reaction is with two equivalents, giving rise to formazans¹²⁶ (Chapter 11) (Eq. 70). In alkaline solution, a third equivalent of diazonium salt acts to replace the nitro group by aryl.¹²⁷ The initial reaction is believed to take place through attack

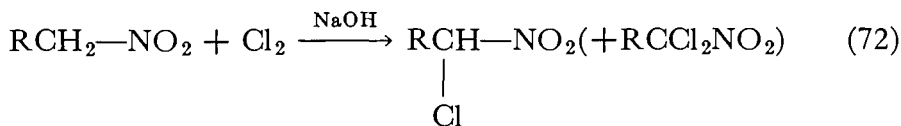


of the diazonium cation on the nitronic acid or its anion.¹²⁶ Nitroalkanes having only one α -hydrogen, and which are therefore superficially restricted to simple formation of an azo compound, in some instances are nevertheless converted to arylhydrazones through migration

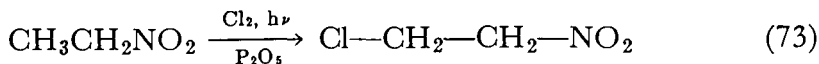


of a nitro group (Eq. 71). Presumably the migration is intermolecular and involves a nitronium ion, NO_2^+ , but the evidence is insufficient; the reaction appears to be general for aryldinitromethanes and diarylnitromethanes.

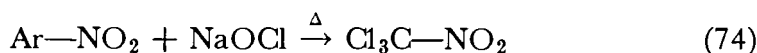
HALOGENATION Like other electrophilic reagents, halogens attack primary and secondary nitroalkanes at the α -carbon, through the nitronic acid form or its anion. Chlorination of primary nitroalkanes in the presence of sodium hydroxide can be controlled so as to give almost exclusively monochloro products¹²⁸ (Eq. 72); on the other hand, chlorina-



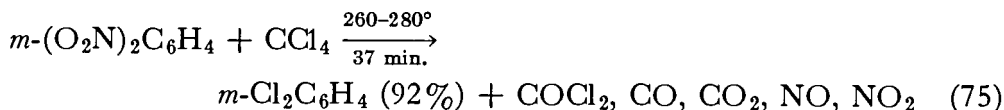
tion of nitromethane can be carried all the way to chloropicrin.¹²⁹ The dependence of base-catalyzed halogenation on the rate of formation of nitronate has been demonstrated by kinetic studies of iodination in the presence of pyridine.¹³⁰ Acid-catalyzed halogenation has also been observed; it is slower than the base-catalyzed process, and its rate appears to depend on the rate of tautomerization to the nitronic acid.¹¹ In a nonpolar environment, electrophilic halogenation is repressed, and free-radical halogenation can be observed; this takes place at a beta or gamma position^{32, 131} (Eq. 73).



Ionic halogenation of nitrobenzenes, like electrophilic substitution in general, is much slower than that of benzene; the relative rates of chlorination of nitrobenzene and benzene ^{132a} are $1.8 \times 10^{-6}:1$. Substitution takes place preferentially *meta* to the nitro group; the isomer ratio for chlorination of nitrobenzene is actually *o*:*m*:*p* = 6.4:93.2:0.3, which reveals a significant susceptibility to *ortho* substitution.^{132b} Deactivation of the ring by the nitro group is markedly less when the steric effect of *ortho* substituents inhibits conjugation by interfering with coplanarity between the nitro group and the ring; nitrodivene, for example, is more easily halogenated than one would estimate simply from the electronic influence of the methyl groups.¹³³ Hypochlorite and hypobromite accomplish destructive halogenation, converting the nitro group and its attached carbon to chloropicrin or bromopicrin ¹³⁴ (Eq. 74). Such reactions have been found useful in investigating isotope-labeling patterns in benzene rings.

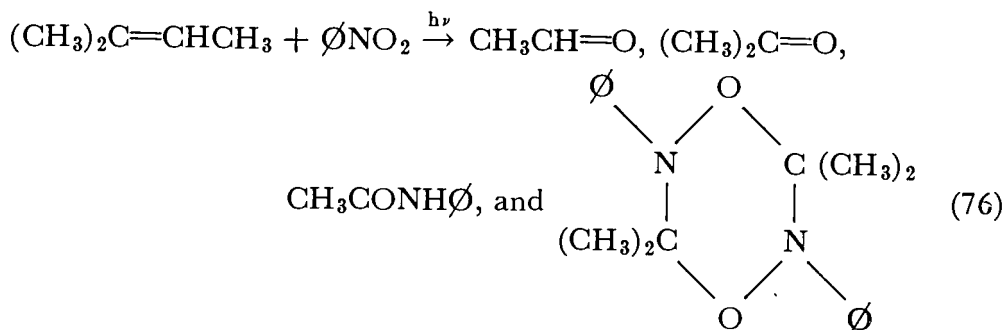


Possible free-radical halogenation of nitrobenzenes takes place at moderately elevated temperatures and replaces nitro groups, not hydrogen, by halogen. Carbon tetrachloride as the halogen source gives very high yields of aryl halides ¹³⁵ (Eq. 75). The same transformation is accom-

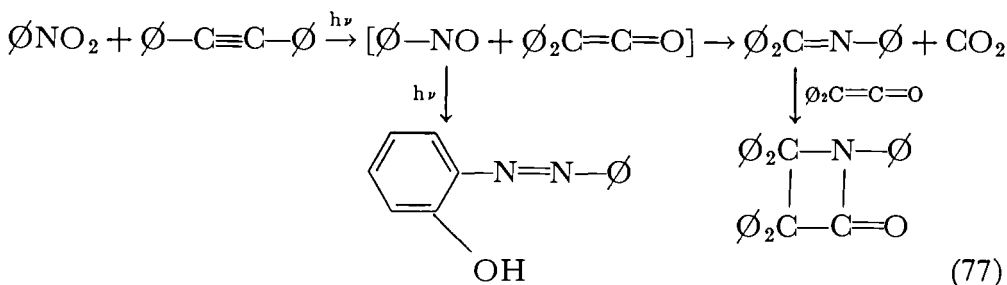


plished at 150–200° by chlorine ¹³⁶ alone or in the presence of ferric chloride, although the latter substance is in general a catalyst for ionic halogenation.

OLEFINS AND ACETYLENES Although the nitro group is ordinarily inert toward carbon-carbon unsaturation, reaction of nitrobenzenes can be induced by ultraviolet irradiation; presumably the photo-excited nitro compound is the active agent. Olefins are cleaved to give oxygenated products analogous to those obtained by ozonization ¹³⁷ (Eq. 76) and a dioxadiazine, which is presumed to derive from a 1:1 dioxazolidine

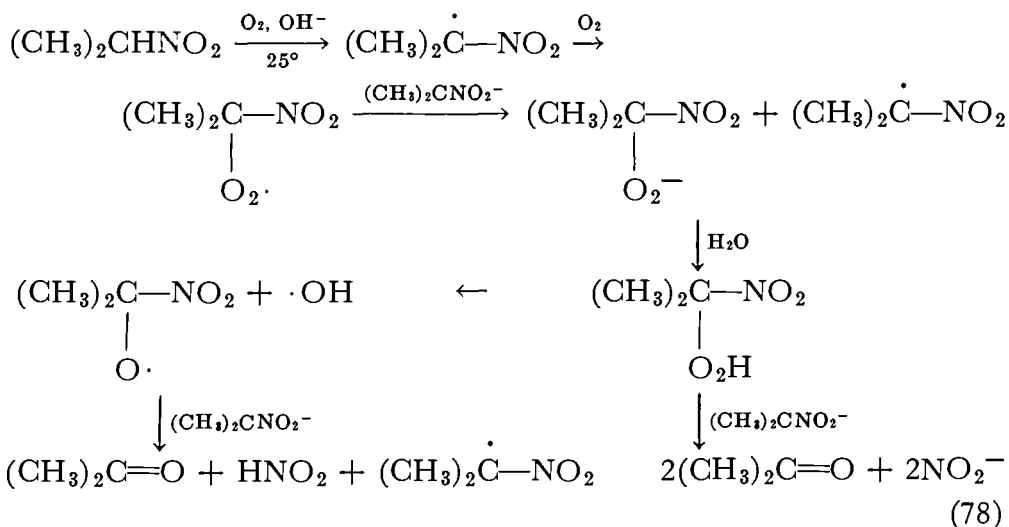


adduct. Under similar conditions, diphenylacetylene gives rise to a variety of products that apparently stem from an initial oxidative rearrangement to diphenylketene ¹³⁸ (Eq. 77). It is also appropriate to

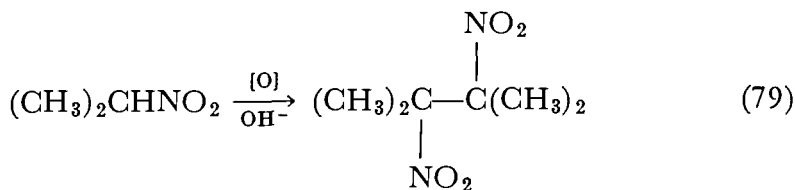


mention at this point the reaction of nitroethylenes with conjugated dienes in the Diels-Alder reaction,^{35, 139} which derives from the activation of the ethylenic double bond through electron withdrawal by the nitro group.

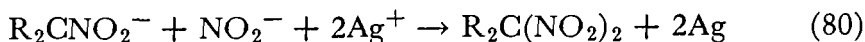
OXIDATION Nitroalkanes are particularly sensitive to oxidation in alkaline solution; even the oxygen of the air attacks them. 2-Nitropropane, for example, is converted largely to acetone and nitrite ion (accompanied by some 2,3-dinitro-2,3-dimethylbutane) by an autocatalytic process that is believed to involve a free-radical chain reaction¹⁴⁰ (Eq. 78). Oxidation with many cupric salts in ammoniacal solution,



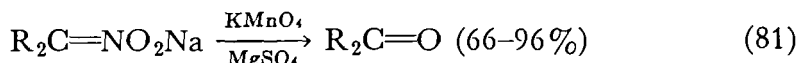
ferric chloride, peroxydisulfate, or sodium peroxide apparently also forms free radicals, which, however, dimerize to *vic*-dinitro compounds ^{140, 141} (Eq. 79). This type of oxidation is intrinsically the same as the decom-



position of silver nitronates, mentioned earlier. When the silver ion oxidation is carried out in the presence of nitrite ion, the reaction path is diverted to the formation of *gem*-dinitro compounds¹⁴² (Eq. 80); regeneration of the silver ion by *in situ* electrolysis makes the reaction economical as well as of preparative value.



Oxidation of nitronate salts with neutral permanganate gives aldehydes or ketones in moderate to good yields¹⁴³ (Eq. 81). This is the same overall transformation as brought about by the Nef reaction, but



the results are claimed to be better, especially with hindered or sensitive compounds.

Aromatic nitro compounds are not unexpectedly inert to oxidation under most circumstances, apart from the oxidative halogenation mentioned earlier, although aliphatic side chains are oxidizable in the ordinary manner.

REDUCTION Of the full range of reduction states between nitro compounds and amines, involving both monomeric and dimeric products, all but nitroso compounds can in general be obtained by suitable control of the reducing conditions. Nitroso compounds are formed too, but since the nitroso group is in general reduced much faster than the nitro group, reduction cannot be stopped to a substantial extent at the nitroso stage. The actual product obtained in a given instance is determined not so much by thermodynamic factors (i.e., oxidation potentials) as by kinetic factors (mechanism and relative rates of competing reactions). The literature on the subject, especially concerning aromatic compounds, is enormous, and only a brief representative survey can be given here.

The simplest reduction is a one-electron transfer to give a radical anion, $\text{RNO}_2^{\cdot-}$. Such radical anions are rapidly formed from aromatic nitro compounds in the presence of strong base, such as potassium *tert*-butoxide, without the addition of any other reducing agent, and can be detected by their electron-spin-resonance signals and can be observed by their colors.^{54, 144, 145} Tertiary nitroalkanes are apparently converted to anion radicals by metallic sodium in an inert solvent; they then break up into tertiary alkyl radicals and nitrite ion, which in turn give rise to the various products isolated. 2-Nitroisobutane gives principally sodium di-*tert*-butylnitronate^{9a} (Eq. 82), but other examples give largely dimers and disproportionation products of the alkyl radical.¹⁴⁶ Disproportionation of the nitronate salt upon the addition of water is a useful preparative method for di-*tert*-butyl nitroxide.

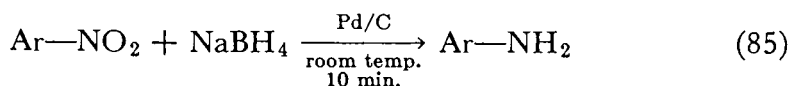
by tying up the hydroxylamine or amine as a cation; formation of dimeric products may also be reduced by use of very vigorous reducing conditions, which do not allow an appreciable concentration of nitroso compound to accumulate. With primary and secondary nitroalkanes, tautomerization of the intermediate nitroso compound to an oxime is usually rapid; as a result, oximes are often obtained, and dimeric products are in any event sharply curtailed.

The scheme of Equation 84 was essentially formulated at the end of the 19th century ¹⁵¹ and is customarily referred to as the Haber mechanism. It is obvious from inspection of the scheme that the formation of a given intermediate reduction product in preparatively significant amounts must be the result of a rather delicate balance of competing reaction rates. Because of this situation, the various methods of reduction are best classified empirically. Methods for obtaining a given type of reduction product are mentioned in the "Preparative Methods" sections of the appropriate chapters; in this chapter, the overall behavior of the more important reagents will be considered.

Sodium alkoxides have long been used to effect reduction of nitrobenzenes to azoxy or azo compounds.¹⁵² Sodium methoxide has been the most commonly selected reagent, but the ethoxide and *n*-propoxide react more rapidly.

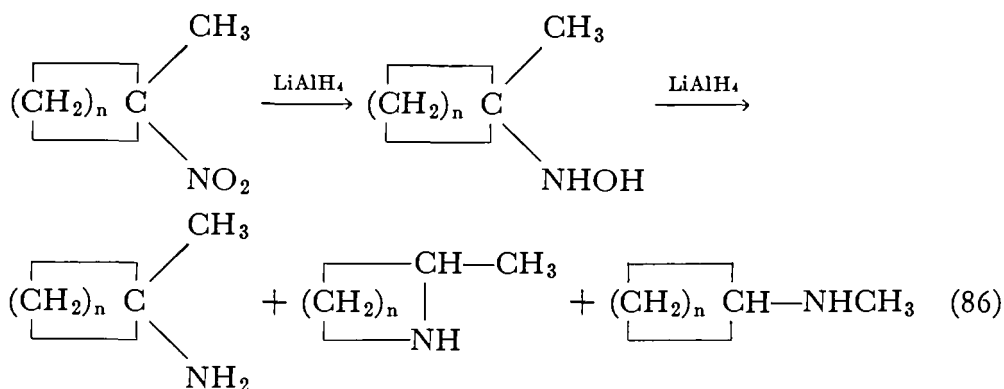
Catalytic hydrogenation,¹⁵³ using Raney nickel,^{154a} platinum oxide,^{154b} or palladium on charcoal,^{154c} generally accomplishes reduction to amines readily. The kinetics have been shown to be characteristic of a surface reaction—first order in nitro compound at low concentrations, zero order at high concentrations.¹⁵⁵ The reaction is highly exothermic and can result in explosion if too much catalyst or too concentrated a solution is used.¹⁵⁶ Catalytic hydrogenation has been successfully stopped at the hydroxylamine stage, however, especially with nitroalkanes,¹⁵⁷ and, in alkaline solution, at the hydrazobenzene stage.^{157a} Hydrogenation of a nitro group may be slower than hydrogenation of a C—C double bond, as illustrated by the successful reduction of a nitroethylene to a nitroalkane.¹⁵⁸

Sodium borohydride reduces aromatic nitro compounds to amines quickly and in good yield in the presence of a palladium catalyst ¹⁵⁹ (Eq. 85). Without a catalyst, sodium borohydride is without action on aliphatic nitro groups,¹³⁹ and there are numerous instances of the successful reduction of other functions by this reagent without disturbing nitro groups. Aromatic nitro compounds are also generally inert, but there are many interesting exceptions. Azoxy compounds may be produced,¹⁶⁰



the aromatic ring may be reduced ^{161, 162} (e.g., TNB yields 1,3,5-trinitro-cyclohexane), or an aromatic nitro group may be replaced by hydrogen.¹⁶³

Lithium aluminum hydride not unexpectedly succeeds where uncatalyzed sodium borohydride fails. It reduces nitroalkanes smoothly to amines at ordinary temperatures,¹⁶⁴ but its action on nitro groups can be quenched at -50 to -60° so as to allow selective reduction of carbonyl groups or conjugated C—C double bonds.¹⁶⁵ Reduction may be vigorous to the point of explosiveness at room temperature, however, and slow addition of the hydride by means of a Soxhlet extractor has been recommended.^{166a} However, addition of hydride to certain cyclic tertiary nitro compounds has been found to promote rearrangement to secondary amines to a substantial extent (Eq. 86); rearrangement appears



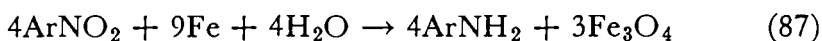
to arise through the alkylhydroxylamines, which are also found among the products ^{166b} (see p. 13).

Lithium aluminum hydride generally reduces aromatic nitro compounds to azo compounds; small to moderate amounts of amines may be formed from *ortho*-substituted nitro compounds, however.^{167a} The azobenzenes that are almost invariably formed from nitrobenzenes are, of course, colored substances, a fact that has led to the use of lithium aluminum hydride as a reagent for the qualitative detection of aromatic nitro compounds.^{167b} The addition of aluminum chloride accelerates reduction by lithium aluminum hydride to lead to aromatic amines fairly generally,^{168a} but addition of ethanol forms a reagent, lithium triethoxyaluminum hydride, that behaves like the parent compound in converting nitroalkanes to amines and nitrobenzenes to azobenzenes.^{168b}

Hydrazine, phenylhydrazine, and methylhydrazine have a long but slender history as reagents for reduction of aromatic nitro compounds to amines.¹⁶⁹ Alone they generally require heating,¹⁷⁰ but in the presence of a palladium-on-charcoal catalyst, reaction takes place at room temperature.^{171, 172} The use of a ruthenium or Raney nickel catalyst produces hydrazo or azoxy compounds¹⁷³; hydrazobenzenes have also been obtained by treatment with hydrazine and a palladium catalyst in the presence of alcoholic alkali.¹⁷⁴

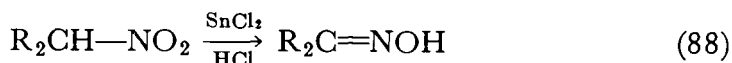
Dissolving metals in some variety reduce nitro compounds; the products are determined more by the conditions than the choice of metal.

Iron filings in the presence of acids or salts have been used widely and successfully to reduce nitro compounds to amines¹⁷⁵; this method is sometimes called Béchamp reduction. It is an economical method that produces fairly clean products in a medium from which isolation is convenient. Impure iron, such as pig iron, is more effective than pure iron. With aromatic nitro compounds, only a catalytic amount of hydrochloric acid is needed, and even that may be replaced by such substances as ammonium chloride or sodium chloride. Under such conditions, the iron is oxidized to its oxide in an easily filterable state,^{176a} according to Equation 87. Iron also reduces nitroalkanes smoothly to amines in high

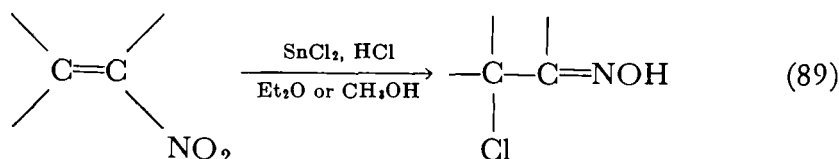


yields, but molar quantities of acid appear to be required^{154a}; iron and acetic acid reduce optically active *sec*-nitroalkanes without destroying the optical asymmetry,^{176b} unlike many other methods of reduction.

Tin in the presence of hydrochloric acid is an old and widely used reagent for the reduction of aromatic nitro compounds to amines.¹⁷⁷ Its reliability and generality commend it, but it has the disadvantage of requiring strongly acidic solutions, which may cause hydrolysis of aliphatic nitro compounds, and frequently cause the intermediate arylhydroxylamines to rearrange to aminophenols and chloroanilines^{178, 179} (cf. Chapter 8). Furthermore, various groups, such as halogen, carboxyl, and even nitro, have been observed to be cleaved off in the process of tin reductions.¹⁸⁰ Stannous chloride is a more satisfactory reagent from the standpoint of versatility of conditions and enables reduction to be carried out in one phase. Aliphatic nitro compounds as well as aromatic are reduced, the former to oximes¹⁸¹ (Eq. 88) or hydroxylamines,¹⁸² the latter to amines. Oximes clearly arise by the acid-catalyzed tautomerization of

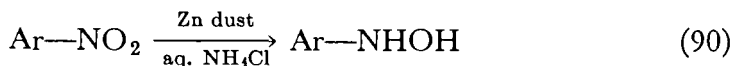


nitrosoalkanes (cf. Chapter 13). Nitro olefins are reduced in good yield to α -chloro oximes¹⁸³ (Eq. 89). Sodium stannite, owing to the con-



comitant alkaline environment, behaves entirely differently and gives azoxy, azo, or hydrazo compounds, according to the relative amounts of reactants.¹⁸⁴

Zinc, customarily used as zinc dust, has seen its principal use in the reduction of nitro compounds in neutral solution, under which conditions it generally gives rise to aryl or alkyl hydroxylamines (Eq. 90). Although there are many reports of successful application,¹⁸⁵ there are

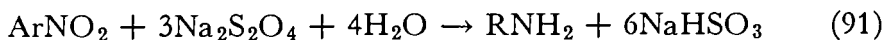


also many reports of frustratingly erratic behavior¹⁸⁶; the quality of the zinc dust may be an important factor, but the significant variable has never been identified. In some instances, high yields of amine have been obtained.¹⁸⁷ In basic solution, aromatic nitro compounds are liable to give hydrazo compounds.¹⁸⁸ Zinc has rarely been used to reduce nitro compounds in solutions more acidic than acetic acid, but an example of successful use of zinc and hydrochloric acid is found in the reduction of 1-piperidino-2-nitrobutane to 1-piperidino-*sec*-butylamine.¹⁸⁹

Aluminum as a reducing agent for the conversion of nitro compounds to hydroxylamines or amines has seen surprisingly little use, considering the generally successful reports and the mildness and convenience of the reactions. Aluminum is generally used lightly coated with mercury by contact with mercuric chloride solution; the procedure for the amalgamation is simple, but of some importance.¹⁹⁰ Water, alcohol, or wet ether are the usual reaction media, and the oxidation product, aluminum hydroxide, is completely innocuous and is easily removed. Yields are usually high, the products are usually clean, and even such sensitive compounds as β -nitro alcohols can be reduced without damage.¹⁹¹⁻¹⁹³

Electrolytic reduction is a generally useful method for converting aromatic or aliphatic nitro compounds to amines,¹⁹⁴ but it can also be controlled to yield principally azoxy, azo, or hydrazo compounds.¹⁹⁵ It was, in fact, the only practical method for the reduction of nitrobenzene directly to azobenzene before the advent of lithium aluminum hydride.

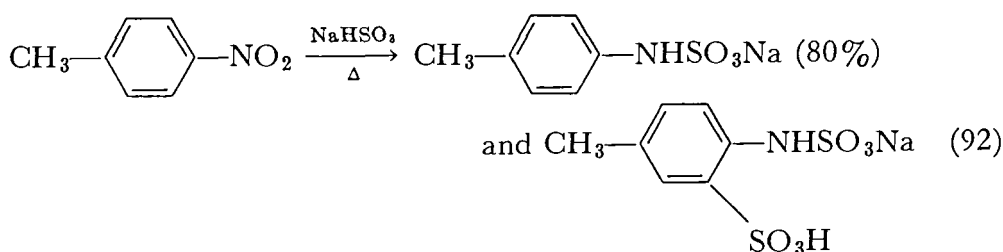
Sodium dithionite (hydrosulfite) has seen only limited use as a reducing agent for nitro compounds, but nevertheless converts them fairly reliably to primary amines¹⁹⁶ (Eq. 91). Sulfamic acids are sometimes



found as by-products and occasionally as major products¹⁹⁷; they arise from reaction of bisulfite with arylhydroxylamine at an intermediate stage in the reduction (cf. Chapter 8).

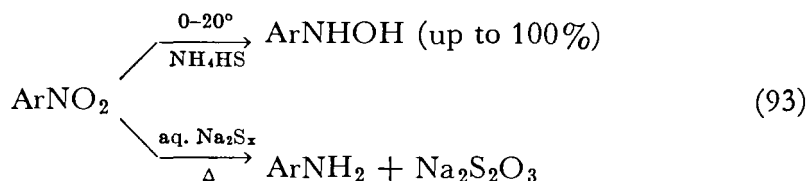
Sulfites themselves will reduce nitro compounds, but not so readily as dithionite; sodium bisulfite is the usual reagent and is used in hot water or methanol. With this reagent, sulfamic acids are commonly major products and are generally accompanied by substantial amounts of

o- or *m*-sulfo sulfamic acids (Piria reaction) (Eq. 92). The sulfonic acids were at one time thought to be rearrangement products of the sulfamic

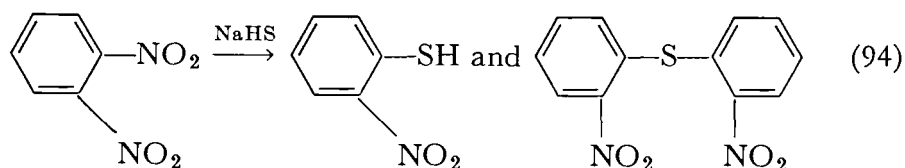


acids, but it was eventually demonstrated that the two types of product arise by competitive, not successive, paths¹⁹⁸; sulfamic acids do not rearrange under the reaction conditions, and when arylhydroxylamines are treated with bisulfite, they are converted to sulfamic acid unaccompanied by any C-sulfonic acid. The C-sulfonic acids must arise by substitution by bisulfite or sulfite ions (or radicals) at an earlier stage (nitrosobenzenes give the same products as nitrobenzenes).

Sulfides, hydrosulfides, and polysulfides are widely used to reduce aromatic nitro compounds to amines.¹⁹⁹ Reduction is very slow in acid solution, but in base (ammonia or alkali), reduction is usually rapid enough to overcome the usual tendency to form dimeric reduction products. The sulfur is usually oxidized to thiosulfate, sometimes free sulfur.²⁰⁰ Reduction is sometimes carried out by bubbling hydrogen sulfide into an alcoholic solution of the nitro compound and ammonia, but polysulfides appear to have the definite advantages of acting faster while still avoiding the excessive alkalinity of sodium sulfide. Time-honored claims that ammonium sulfide preferentially reduces *ortho*-substituted nitro compounds are apparently without foundation.²⁰¹ Sulfides and polysulfides usually require heating to carry reduction all the way to the amine stage; when used at or below room temperature, reduction is slow, but can give good yields of hydroxylamines¹⁸⁶ (Eq. 93). Azo and azoxy compounds



have occasionally been encountered as by-products in sulfide reductions. When easily displaced groups are present in the molecule, mercaptans and/or sulfides may become major products,²⁰⁰ such as in the case of *o*-dinitrobenzene (Eq. 94). Nitrocyclodecane, as its nitronic acid tautomer, is reduced by hydrogen sulfide to the oxime in high yield.^{185b}

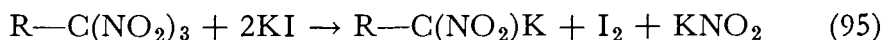


Titanous chloride, chromous chloride, as well as stannous chloride, can be so handled as to reduce aromatic nitro compounds quantitatively to amines and thus provide a means of volumetric analysis for nitro groups.^{202, 203} Reduction is customarily carried out in hot acidic solution, and the excess of reducing agent is back-titrated with a standard oxidizing agent. Chromous chloride reduces nitroalkanes to oximes.²⁰⁴

Ferrous hydroxide has been the subject of a detailed investigation of the relation between experimental conditions and the nature of the reduction products of nitrobenzene.¹⁹⁵ As a reducing agent it has a high specificity for nitro groups and has been widely used for qualitative analysis purposes. Anilines can be obtained nearly quantitatively, but by adjustment of conditions, azoxybenzenes or hydrazobenzenes can be made the major products.

Sodium has seen relatively little use as a reducing agent for nitro compounds, although sodium amalgam will generally reduce them. Sodium in liquid ammonia has been found to reduce nitroalkanes to hydroxylamines slowly and in low yields.²⁰⁵

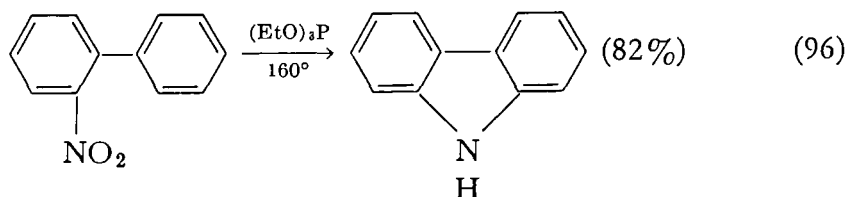
Inorganic iodide does not ordinarily reduce nitro compounds, but has been reported to have specific action on 1,1,1-trinitroalkanes^{206a} (Eq. 95). Hydrogen peroxide in alkaline solution, among other reducing



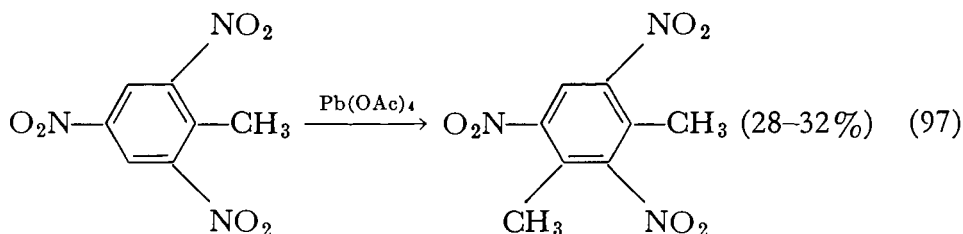
agents, also cleaves one nitro group from such compounds^{206b}; the inorganic products are nitrite and a colorless gas, presumably oxygen.

Nitrobenzene has seen fairly wide use as a hydrogen acceptor in aromatizing dehydrogenations, such as the Skraup reaction, with or without the addition of a hydrogenation catalyst. The catalytic reactions have usually been assumed to involve liberation of hydrogen, which was subsequently removed by reaction with the nitro group with consequent shift of the equilibrium. It has been shown with the example of cyclohexene, however, that hydrogen is not an intermediate, but the nitro group reacts directly with the hydrocarbon.²⁰⁷

Relatively little study has been made of the reaction of nitro compounds with reagents that function primarily as deoxygenating agents. Triethyl phosphite apparently acts in this way, for it converts *o*-nitrobiphenyl to carbazole in high yield²⁰⁸ (Eq. 96); ferrous oxalate accomplishes the same result at somewhat higher temperatures.²⁰⁹

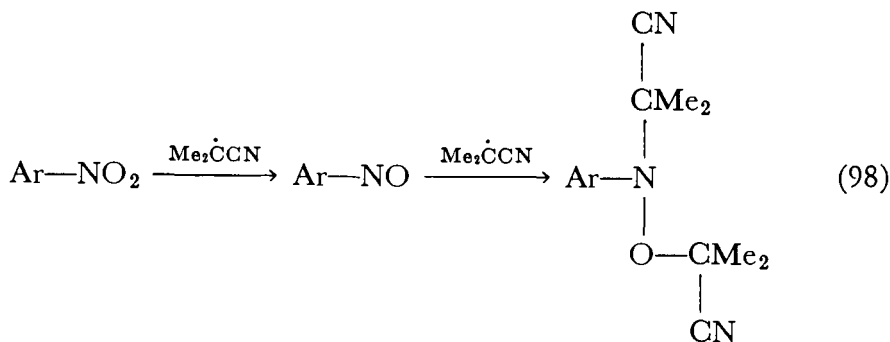


FREE-RADICAL REACTIONS The reactions of free-radical species with nitro compounds have been more thoroughly investigated with aromatic compounds than aliphatic. Apart from the free-radical replacement of $-\text{NO}_2$ by $-\text{Cl}$ already discussed, free radicals may attack either a ring carbon, or the nitrogen or oxygen of a nitro group. Free-radical arylation of nitrobenzene by diazonium compounds and derivatives, which gives more *ortho*- and *para*-substitution than *meta*,²¹⁰ is discussed in Chapter 11. Methyl radicals, generated from peroxides or lead tetraacetate, also attack the ring, giving rise to nitrotoluenes²¹¹ (Eq. 97). Competitive



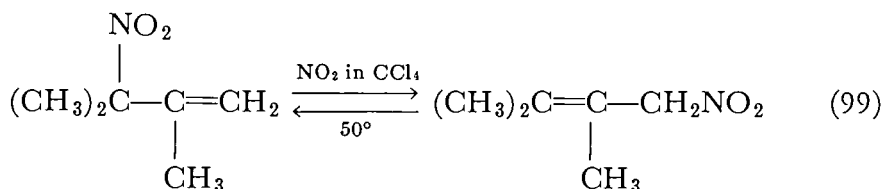
methylation of various aromatic compounds by methyl radicals allows the relative reactivities to be expressed as "methyl affinities"²¹²; that of nitrobenzene is 80 with respect to benzene = 1, and the dinitrobenzenes have values over 500. It is evident that the nitro group is a strong activator for free-radical attack, but it should be noted that it is markedly less effective than the nitroso group (cf. Chapter 13).

In contrast to methyl radicals, cyanoisopropyl radicals (derived from azoisobutyronitrile) attack the nitro group instead of carbon.²¹³ The nitro compound is converted to an O,N-disubstituted phenylhydroxylamine, the same sort of product as would be obtained from the corresponding nitroso compound, which, indeed, is believed to be an inter-

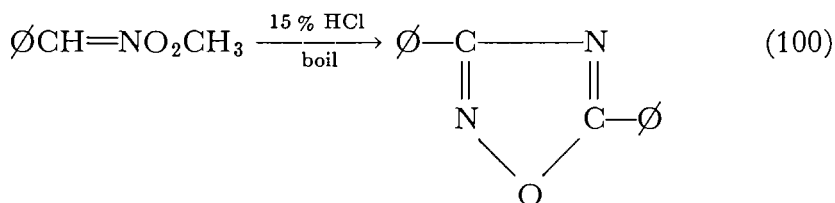


mediate (Eq. 98). Similar results have been observed in the photochemical reaction of nitrobenzene with benzaldehyde, which gives O,N-dibenzoylphenylhydroxylamine,²¹⁴ and in the reaction of benzyl radicals (derived from toluene and di-*tert*-butyl peroxide) with nitrobenzene or TNB.²¹⁵

Nitroalkanes presumably react with alkyl radicals, since they inhibit free-radical polymerization, but the nature of the reaction is uncertain.²¹⁶ Nitrogen dioxide, a free-radical reagent, causes allylic isomerization of conjugated nitro olefins, presumably through reversible addition to form dinitroalkyl radicals²¹⁷ (Eq. 99).

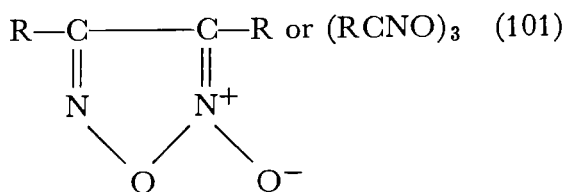
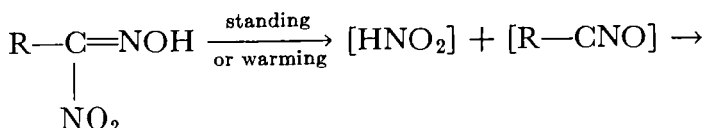


REACTIONS OF NITRONATE ESTERS The dominant reaction of nitronate esters is their decomposition on standing or warming to form an oxime and an aldehyde, accompanied by a variety of other products.⁸ Nitronate esters have not been successfully hydrolyzed so as to regenerate the parent nitronic acid or nitroalkane. Boiling with hydrochloric acid produces oxadiazoles⁹³ (Eq. 100); the same type of product sometimes

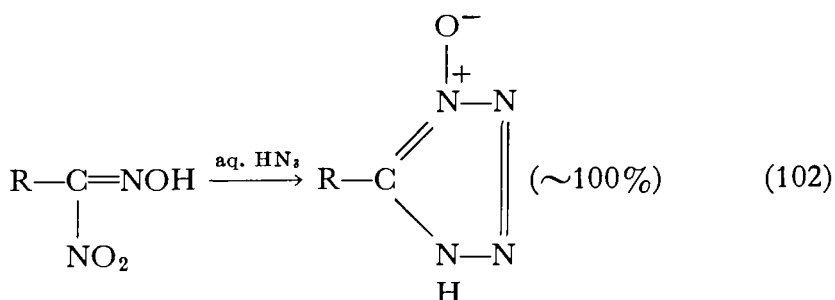


accompanies the oximes formed by simple thermal decomposition. Hydrolysis to an aldehyde (in 4N sulfuric acid) or to a hydroxamic acid (in 85% sulfuric acid) has also been observed.⁸ Some nitronate esters, especially those having an acyl substituent on the α -carbon, have been observed to liberate iodine from concentrated hydriodic acid, but the resulting products were not identified.

REACTIONS OF NITROLIC ACIDS Nitrolic acids are only moderately stable and generally decompose on warming, prolonged storage, or treatment with sodium carbonate by elimination of the elements of nitrous acid; the nitrile oxides that result rapidly form trimers or dimerize to form furoxans^{5, 218} (Eq. 101). The nitrile oxides can be intercepted if the decomposition is allowed to take place in the presence of an acetylene²¹⁹; the resulting reaction is a preparatively useful source of isoxazoles.



Nitrolic acids react spontaneously with aqueous hydrogen azide to give tetrazole-N-oxides ²²⁰ (Eq. 102), which have also been suggested to arise



through interception of a nitrile oxide. Hydrolysis of nitrolic acids gives the corresponding carboxylic acid, hydroxylamine, and nitrous acid or its decomposition products.³⁰ Reduction gives hydroxyamidoximes ²²¹ or amidoximes.²²² Thermal decomposition of nitrolate salts under xylene gives isocyanates in useful yield through isomerization of the nitrile oxides first formed.^{218, 223}

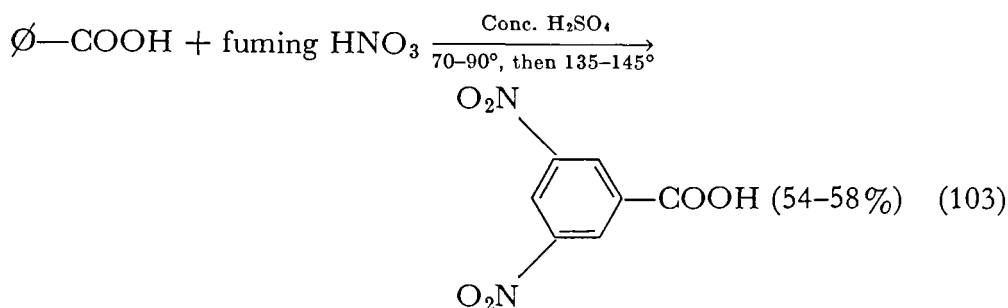
PREPARATIVE METHODS

A. Aromatic Nitro Compounds

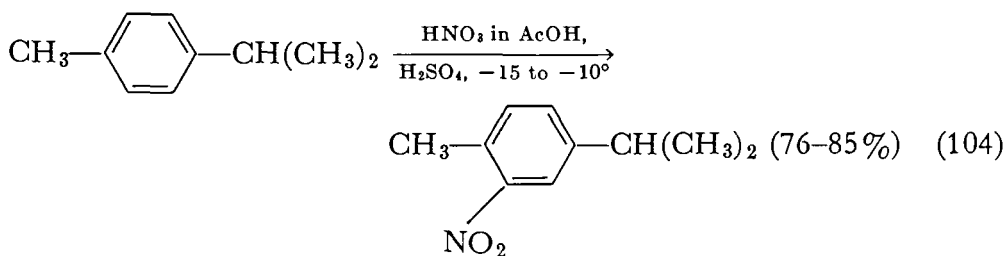
There are four principal types of reaction by which a nitro group may be introduced into an aromatic system: direct nitration; oxidation of anilines, anilides, or aromatic nitroso compounds; replacement of a diazonium group; and condensation of pyrylium salts with nitromethane. The first of these methods is overwhelmingly the most important.

Nitration ²²⁴⁻²²⁶ of aromatic hydrocarbons and their derivatives is traditionally carried out with nitric acid in a medium whose acidity may be varied widely to suit both the reactivity of the substrate and the extent of nitration desired. For compounds resistant to electrophilic attack, this may mean treatment with a mixture of sulfuric and fuming nitric acids at elevated temperatures; the preparation of 3,5-dinitro-

benzoic acid ²²⁷ (Eq. 103) and 2,4,7-trinitrofluorenone ²²⁸ are examples.



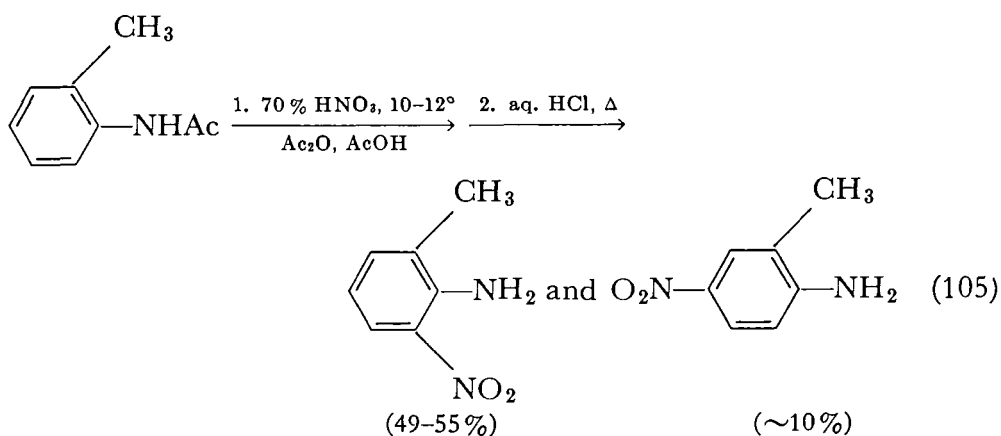
Similar conditions are required for the nitration of β -picoline-N-oxide to its 4-nitro derivative.²²⁹ With increasing reactivity of the ring, both lower temperatures and more dilute acid are indicated, as in the nitration



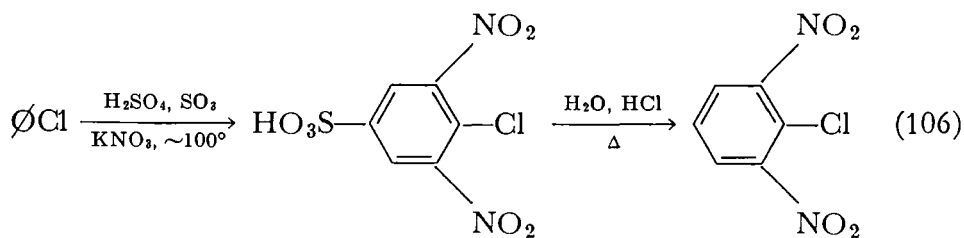
of *p*-cymene ²³⁰ (Eq. 104) and veratraldehyde.²³¹ The effect of substituents on reactivity toward nitration has been correlated by the Hammett equation,²³² and the reaction constant, ρ , has the large value -7.22 . A large number of additional examples of aromatic nitration is to be found in the various volumes of *Organic Syntheses*.

The selection of conditions for aromatic nitration is influenced not only by the reactivity of the substrate, but also by the orientation desired. Most substituents direct an entering nitro group either to the *meta* position or the *para* position, according to the electronic character of the substituent, except that unbranched groups direct *ortho* to themselves to a major extent. The ratio of *ortho* nitration to *para* nitration ²³³ for toluene, for example, is about 1.7 and that of ethylbenzene is about 0.9, but for *tert*-butylbenzene, in which steric hindrance to *ortho* substitution is appreciable, the ratio falls to 0.1–0.2. These ratios are affected but little by the nature of the nitrating medium. Nitration in the presence of acetic anhydride (thus with acetyl nitrate) is widely used because of the exceptional activity of this reagent, which enables very mild conditions to be used. Acetyl nitrate has long been supposed to favor *ortho* nitration, but with the alkylbenzenes, at least, no difference in the nature of the products has been observed,²³³ although such an *ortho*-nitrating effect

may hold for methoxy groups ^{234a} and amido groups, as in the nitration of aceto-*o*-toluidide ^{234b} (Eq. 105). Nitration by means of alkyl nitrates in polyphosphoric acid, by contrast, gives a markedly lower proportion of *ortho* nitration with toluene.²³⁵

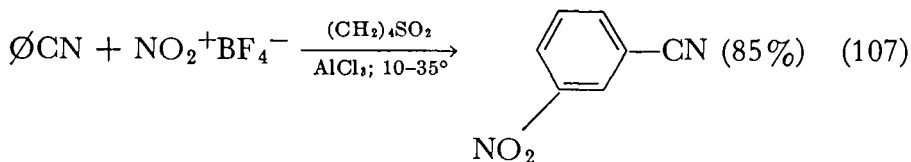


Orientation may also be influenced by the acidity of the medium when basic substituents are present. Dimethylaniline, for example, which ordinarily undergoes *para* substitution, is nitrated in the *meta* position in 56–63% yield in concentrated sulfuric acid,²³⁶ in which the dimethylamino group is effectively entirely protonated and thus functions as a *meta*-directing substituent (cf. Chapter 3). Orientation may also be influenced by first sulfonating the substrate; in this way the most reactive position is blocked. Chlorobenzene may be converted into its 2,6-dinitro derivative by this device, the sulfonic acid substituent being subsequently removed hydrolytically ²³⁷ (Eq. 106).



The high acidity and hydroxylic nature of most nitrating media have the disadvantage of affecting other functional groups, especially hydrolyzable ones, such as cyano and carboethoxy. These disadvantages may be avoided by use of aprotic nitrating agents under Friedel-Crafts conditions.^{238a} Nitronium fluoborate, nitryl chloride, or dinitrogen tetroxide in the presence of aluminum chloride give high yields of nitrobenzene derivatives at mild temperatures (Eq. 107). Trifluoroacetic anhydride

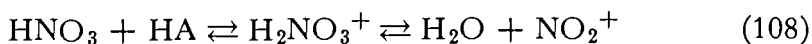
also provides an essentially nonhydrolytic medium in which nitration is effective and fast.^{238b}



The mechanism of nitration²³⁹ has been essentially revealed by kinetic studies in relation to the acidity of the nitrating medium and spectroscopic indications of the species present in it. Two paths for nitration emerge: ordinary nitration, which introduces a nitro group directly, and nitrosative nitration, in which the nitro group is formed by oxidation of a nitroso group first introduced.

Ordinary nitration is observed with most aromatic substances that do not bear highly activating substituents. The kinetics are ordinarily second order,^{239, 240} and the rate is increased by increasing sulfuric acid concentration up to a maximum at about 90% sulfuric acid or equivalent value of the Hammett acidity function H_0 . Increase in acidity beyond this level has relatively little effect, although some retardation may become evident at very high acidities.²⁴¹ These observations are consistent with the necessity to generate nitronium ion, NO_2^+ , as the active nitrating agent. The formation of nitronium ion is very fast in aqueous or sulfuric acid solutions, but in organic solvents, such as nitromethane, becomes slower than the rate of its reaction with the more reactive aromatic compounds.²⁴² Under such circumstances, the rate becomes first order as long as an excess of nitric acid is present, and does not depend on the concentration of the aromatic substrate. The essential role of nitronium ion as the active nitrating agent has also been demonstrated by comparing the rate of ^{18}O isotope exchange between water and nitric acid with the rate of nitration of very active aromatic rings under conditions where the rate is of zero order with respect to the substrate; the rates of exchange and of nitration were the same within experimental error.²⁴³

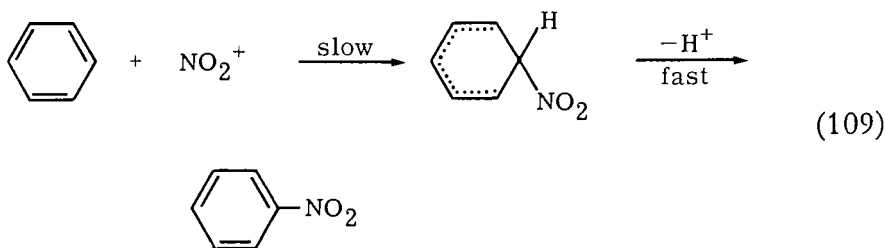
Nitronium ion required for nitration is generated in two stages by the reaction of a strong acid (which may be nitric acid itself) with nitric acid (Eq. 108). The first stage, being a simple proton transfer, should in



general be very fast; the second stage may evidently be slower than the subsequent nitrating step under favorable circumstances. There is no evidence that nitric acidium ion (H_2NO_3^+) functions significantly as a nitrating species under ordinary conditions. In concentrated sulfuric

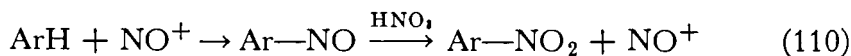
acid solution, nitric acid exists almost entirely as nitronium ion; in 100% nitric acid, a much less acidic environment, about 3–4% of the nitrogen is present as nitronium ion.^{239, 240, 244}

The nitrating step has been demonstrated in various ways to involve a slow attack on the aromatic ring to produce a true intermediate,²⁴⁵ a sigma-complex, which loses a proton rapidly to form the product (Eq. 109). The most convincing evidence for this state of affairs is the com-



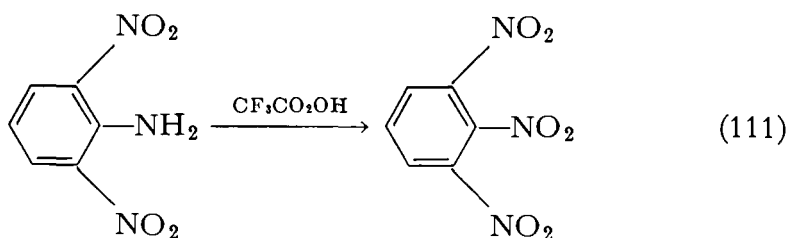
plete absence of a deuterium or tritium isotope effect on the rate of nitration.^{246, 247}

Although nitrous acid (i.e., substances such as N_2O_4 , N_2O_3 , etc., that hydrolyze to nitrous acid on dilution) generally retards nitration, owing to removal of nitronium ion, it acts as a catalyst for the nitration of very reactive aromatic compounds, notably anilines and phenol ethers. The catalysis has been shown to operate by providing a new path to the nitro compound through nitrosation followed by rapid oxidation^{239, 248} (Eq.



110). It is observed with these substances because they are so active that the nitrating conditions must for practical reasons be very mild, which implies low acidity and a low concentration of nitronium ion. Even though nitrosonium ion is a less active electrophilic agent than nitronium ion, it can compete because of the much greater equilibrium concentration of it at equivalent acidities. When nitrous acid is strictly excluded, ordinary nitration through nitronium ion takes over.

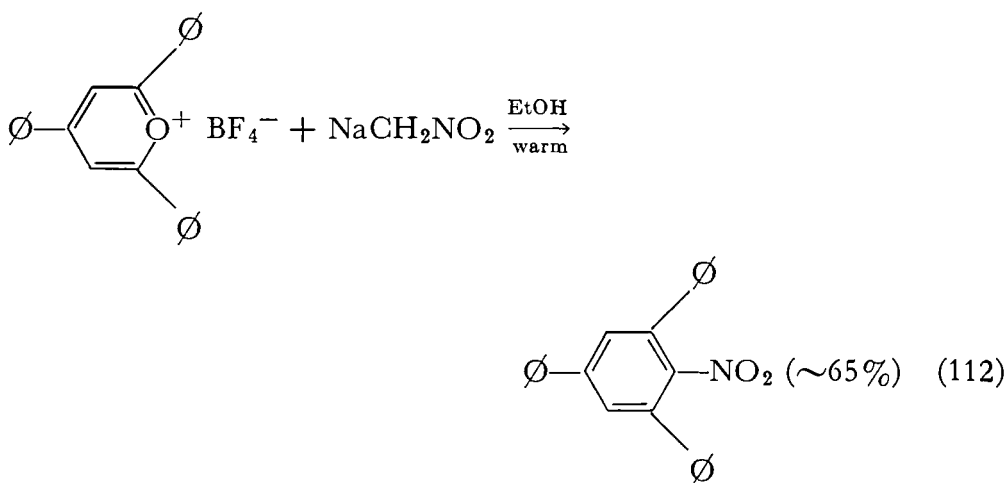
The preparation of aromatic nitro compounds by oxidation of anilines is ordinarily limited to those situations where direct nitration does not give the required isomer; the preparation of *p*-dinitrobenzene from *p*-nitroaniline is an example.²⁴⁹ Oxidation is usually accomplished by peroxy acids (cf. Chapter 3), with or without the isolation of the intermediate nitroso compounds. Oxidation is fairly generally successful and is not prevented even by the considerable steric interference encountered in 2,6-dinitroaniline²⁵⁰ (Eq. 111). Similar results have been obtained by



oxidizing anilides, particularly formanilides, with hydrogen peroxide in hot acetic acid.²⁵⁰

Replacement of an aromatic amino group by nitro through diazotization and treatment with nitrite salts is occasionally very successful and gives nearly quantitative yields of *ortho*- and *para*-dinitrobenzenes,²⁵¹ but is far from general (cf. Chapter 11).

The reaction of pyrylium salts with nitromethane, in which a benzene ring is formed by replacing the pyrylium oxygen by carbon²⁵² (Eq. 112), is more practical than its bizarreness might suggest and in some instances is the method of choice.

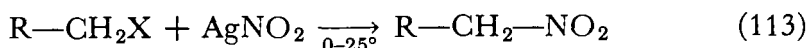


Methods of preparing aromatic nitro compounds other than by nitration, including methods of securing special orientation by the use of auxiliary blocking or orienting substituents, have been reviewed.²⁵³

B. Aliphatic Nitro Compounds²⁵⁴

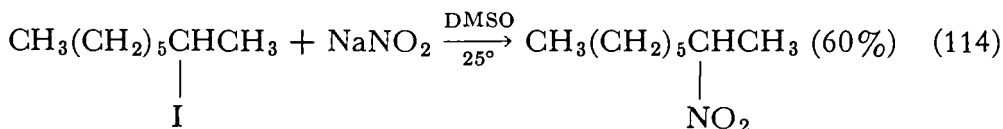
Aliphatic nitro compounds can be prepared by reaction of alkyl halides with nitrite salts, by oxidation of amines or functions of intermediate oxidation state (especially oximes), by nitration of saturated hydrocarbons, olefins, or active methylene compounds, and by alteration of compounds already containing nitro groups. The first of these methods is the most important for laboratory preparation.

The reaction of alkylating agents with silver nitrite, usually known as the Victor Meyer reaction, yields nitroalkanes along with more or less significant quantities of alkyl nitrate, alkyl nitrite, alcohol, and carbonyl compounds.⁷ It is a preparatively useful reaction for primary nitroalkanes (Eq. 113); alkyl bromides and iodides give clean products in good yields, but chlorides are inactive.²⁵⁵ Secondary alkyl halides give



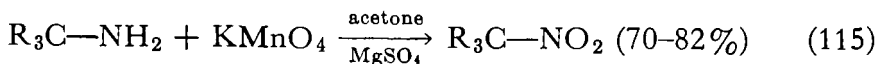
poor yields of nitroalkanes that are difficult to purify; the contaminants apparently arise from an elimination reaction that releases nitrous acid, which in turn disproportionates and gives rise to silver nitrate, etc.²⁵⁶ Tertiary alkyl chlorides give nitrite esters rather than nitroalkanes, and tertiary alkyl iodides liberate iodine. The alkylation of silver nitrite takes place with optical inversion,²⁵⁷ or, when structure favors an S_N1 path, with racemization.

Alkylation of sodium nitrite gives mixtures with nitrite esters in which the nitro compound is usually the major component. Primary and secondary alkyl bromides or iodides give good yields if the reaction is carried out in dimethylformamide or dimethyl sulfoxide as a solvent²⁵⁸ (Eq. 114); a nitrite scavenger (phloroglucinol is best) is necessary to prevent nitrosation of the product by the alkyl nitrite produced. Tertiary alkyl halides undergo elimination and give no nitrite or nitro compound



by this method. α -Halo esters, which do not react well with silver nitrite, give good yields of α -nitro esters²⁵⁹; here this reaction is the method of choice. Even some tertiary α -nitro esters have been made in this way.

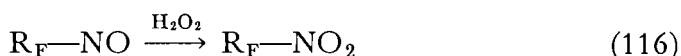
Oxidation of amines (cf. Chapter 2) is a valuable method for preparing tertiary nitroalkanes, which cannot in general be prepared by the alkylation method. Potassium permanganate gives good yields of nitro compound from tertiary-alkyl amines^{166b, 260} (Eq. 115), but fails when the alkyl group is primary or secondary. Peroxyacetic acid has given good



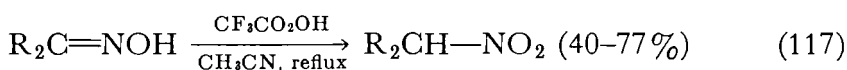
yields of nitroalkanes from some primary amines having primary or secondary alkyl groups,²⁶¹ but the method has not been widely explored.

Oxidation of nitroso compounds is not ordinarily considered to be a significant preparative method for nitroalkanes, not only because of the

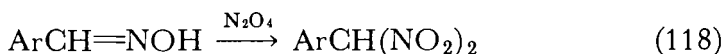
instability of most primary and secondary nitroso compounds, but because of the difficulty in obtaining them. Perfluoronitroso compounds, however, are stable and moderately readily obtained; oxidation to perfluoronitroalkanes is accomplished by hydrogen peroxide ²⁶² (Eq. 116).



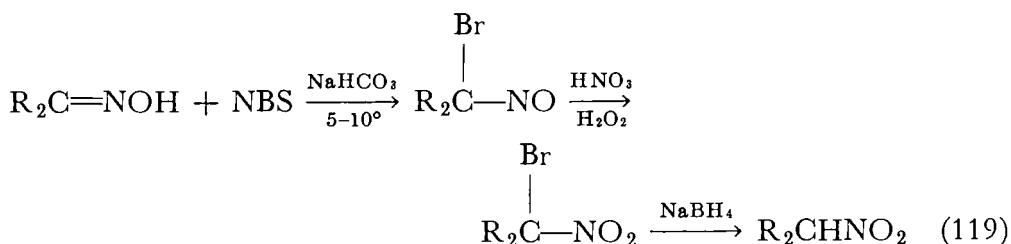
Oxidation of oximes, which may be accomplished by two distinct routes, provides a preparative method for primary and secondary nitroalkanes of wide generality. Peroxytrifluoroacetic acid gives good yields of nitro compounds from aldoximes and ketoximes that are not sterically hindered ²⁶³ (Eq. 117). Nitratative oxidation of oximes with nitrogen



tetroxide provides a good route to *gem*-dinitro compounds ^{121b} (Eq. 118). Conversion of oximes to mononitro compounds can alternatively be



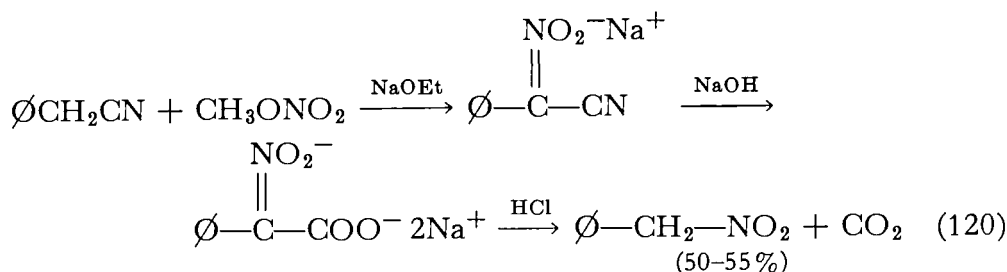
accomplished in a three-step sequence of bromination with N-bromosuccinimide, oxidation, and reductive debromination with sodium borohydride, in overall yields up to 55% ²⁶⁴ (Eq. 119). Although the yields are in general not as good as those from direct oxidation, the method has



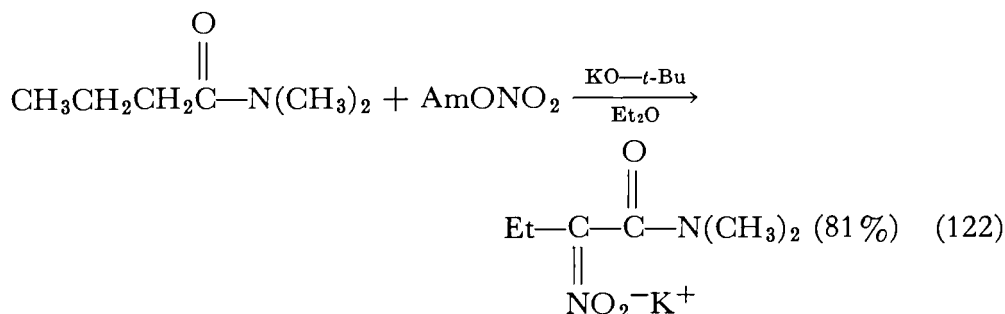
the advantage of succeeding with sterically hindered oximes where direct oxidation fails.

Replacement of an aliphatic hydrogen by a nitro group is satisfactory for laboratory preparation only in limited circumstances. It is most successful with hydrogens of the active methylene type, which may fairly generally be replaced by nitro with alkyl nitrates and a strong base ²⁶⁵; nitric acid and nitrogen tetroxide have also been used. Arylacetonitriles ²⁶⁶ and arylacetic esters ²⁶⁷ are easily susceptible to alkaline nitration, by which they are converted to arylnitromethanes (Eqs. 120, 121),

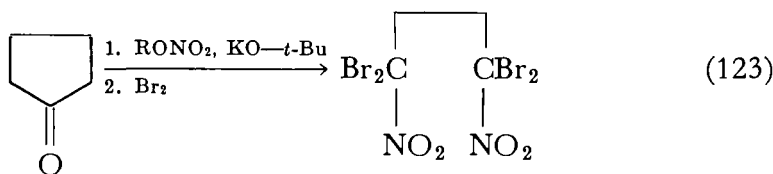
but even simple nitriles,²⁶⁸ ketones,²⁶⁸ and even amides²⁶⁹ (Eq. 122) can



be nitrated in good yields. When cyclic ketones are subjected to this



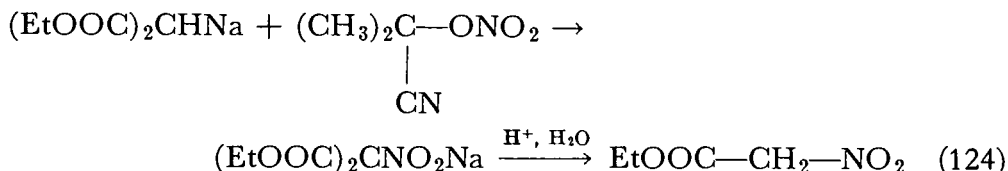
reaction, and, as is frequently done, the nitronate salt is treated with bromine to give a stable, easily isolable product, the ring is opened (Eq. 123). Potassium ethoxide is said to be superior to sodium ethoxide as a



condensing agent, but potassium *t*-butoxide suspended in tetrahydrofuran is the most powerful, and its use is indicated for the less powerfully activated sites.

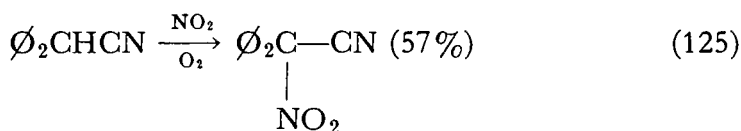
Alkaline nitration is a nucleophilic displacement reaction taking place on nitrogen (cf. Chapter 15). The α -carbon of alkyl nitrates is also susceptible to nucleophilic displacement, however, thereby giving rise to alkylation instead of nitration. Alkylation becomes the dominant process in the reaction of the carbanions of malonic and acetoacetic esters with simple alkyl nitrates, but this difficulty can be overcome by using α -cyanoisopropyl nitrate (acetone cyanohydrin nitrate) instead.²⁷⁰ The

reaction then becomes a general route to α -nitro esters (Eq. 124), although

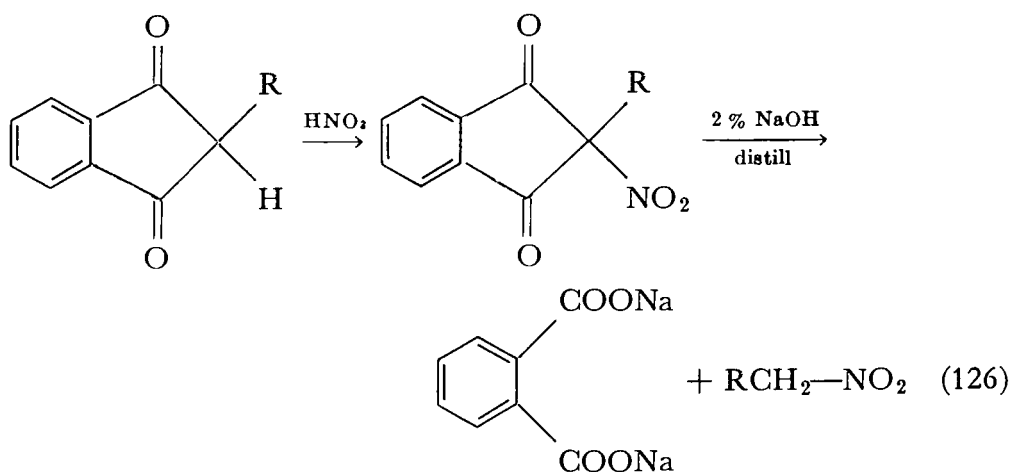


results are generally inferior to those of the α -halo ester-sodium nitrite route.

Nitration of active methylene compounds may be accomplished with concentrated or fuming nitric acid near room temperature^{93, 271}; yields can be high (nitromalonic ester, 92%), but the products must be treated with urea to remove traces of oxides of nitrogen that catalyze their decomposition. Nitration with nitrogen dioxide, used in solution in chloroform or carbon tetrachloride in the presence of oxygen and sometimes copper sulfate, gives moderate yields^{272, 273} (Eq. 125); it is apparently a free-radical reaction.

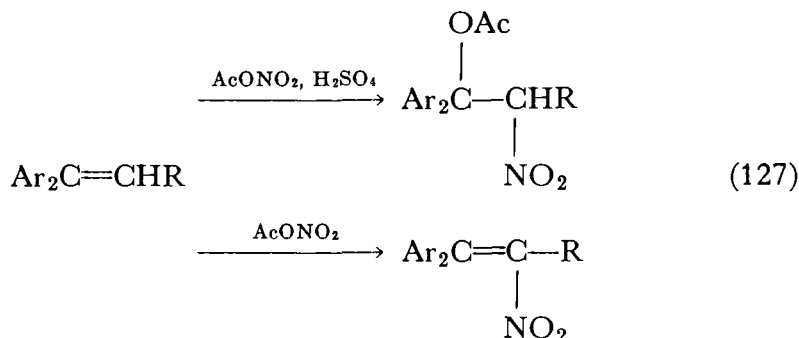


Nitration of active methylene compounds has been combined with the alkaline cleavage of α -nitro ketones to give a synthesis of considerable generality for simple primary nitroalkanes; indandiones, which are easily available, play the essential role²⁷⁴ (Eq. 126).



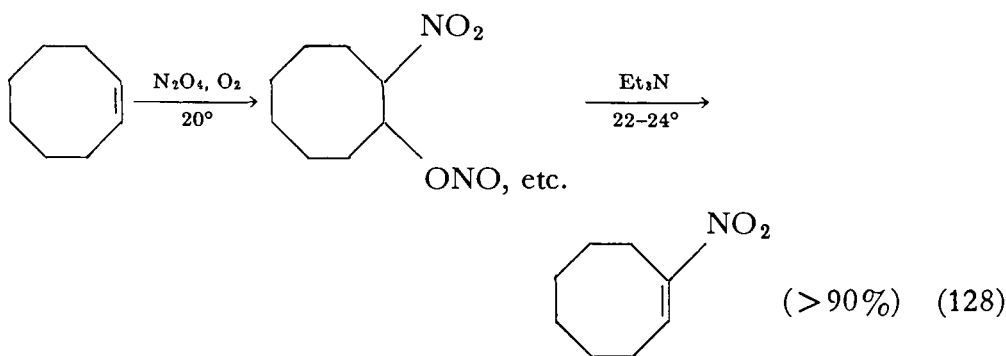
Nitration of olefins can be accomplished in several ways. Direct nitration with cold, ethereal nitric acid, which yields nitro olefins, has been used particularly in the steroid field.²⁷⁵ Nitration with acetyl

nitrate usually gives β -acetoxy nitro compounds by a *cis*-addition mechanism, but nitro olefins sometimes predominate when the reaction is carried out in the absence of sulfuric acid ^{234, 276} (Eq. 127). Low yields of nitro olefins have been obtained by treatment of simple olefins with

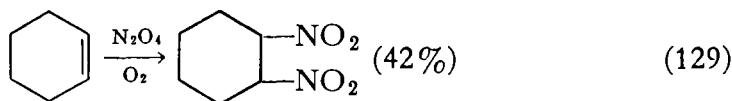


nitric oxide at room temperature under pressure.²¹⁷

Olefins have been nitrated stepwise by treatment with nitrogen tetroxide in the presence of oxygen, followed by an elimination reaction induced by triethylamine; although the first step produces a mixture of *vic*-dinitro compounds, β -nitro nitrites, and β -nitro nitrates, the overall conversions to nitro olefins are high ⁵⁵ (Eq. 128). The addition step can be so conducted as to give moderate but useful yields of *vic*-dinitro

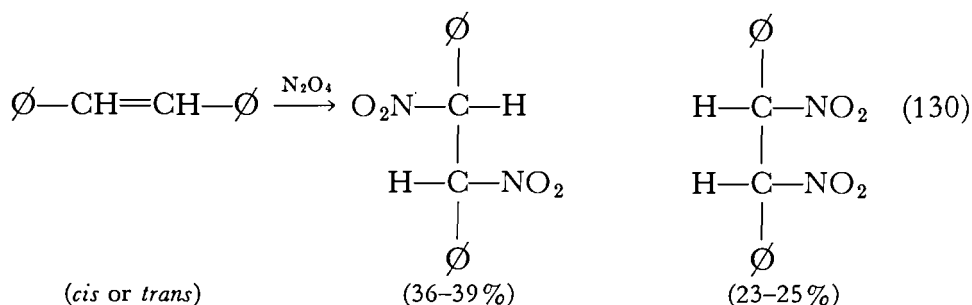


compounds ^{276, 277} (Eq. 129). The addition of nitrogen tetroxide (and/or dioxide) has been shown to be a free-radical process by examining the

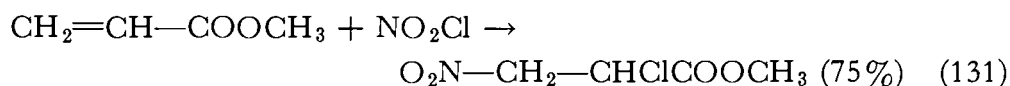


orientation of the β -nitro nitrites and β -nitro nitrates that are generally the predominant products.²⁷⁷ The nitro group is always found attached to the least substituted carbon, regardless of the polarity of other sub-

stituents; methyl acrylate, for example, gives β -nitropropionic acid derivatives.²⁷⁸ This type of reaction proceeds best in oxygen-containing solvents, particularly cyclic ethers, which appear to catalyze reaction through formation of adducts with N_2O_4 . The initial attack is presumably by NO_2 to give a β -nitroalkyl radical, in agreement with which is the observation that addition has no stereospecificity (*cis*- and *trans*-stilbene give the same product, largely d,l-1,2-dinitro-1,2-diphenylethane)²⁷⁹ (Eq. 130). These reactions closely resemble the addition of nitrous anhydride



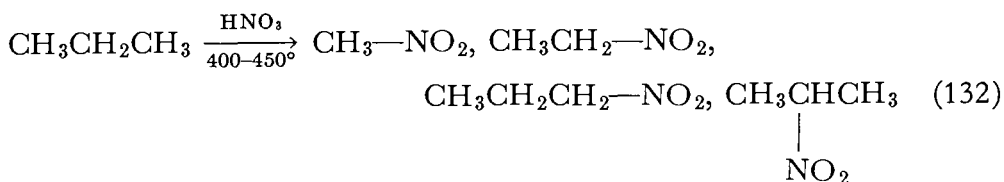
to olefins, which gives β -nitroso nitro compounds (pseudonitrosites) by a free-radical path²⁸⁰ (cf. Chapter 13). Addition of nitryl chloride to olefins, which gives β -chloro nitro compounds (Eq. 131) is also a free-



radical reaction.²⁸¹ β -Iodo nitro compounds can be obtained by the mechanistically analogous reaction of olefins with nitrogen dioxide and iodine.²⁸²

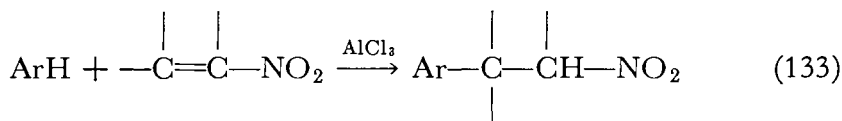
The nitration of saturated aliphatic hydrocarbons is of exceptional importance commercially for the bulk production of the smaller nitroalkanes,³² but for various reasons is of little significance as a laboratory method. Liquid-phase nitration was investigated extensively by Konovalov and associates in the early part of this century; this work has been reviewed in detail elsewhere.³³ The reaction proceeds best at temperatures of 120–140° and thus usually requires a sealed tube or acid-resistant autoclave. Primary hydrogens are essentially inert to attack, and tertiary hydrogens are attacked most easily. The reaction is a free-radical process, in which NO_2 is the active agent^{283, 284}; early conclusions that optical asymmetry is retained at the site of nitration have been shown to be untenable. Alkyl side chains of alkylbenzenes can be nitrated at the α -carbon in this way if dilute nitric acid is used to minimize ring nitration.²⁸⁵ Vapor-phase nitration, which is used industrially, takes place in the uncomfortable temperature range 400–450° and results in extensive fragmentation of the carbon skeleton³²; products are obtained from the

breaking of every possible C—H or C—C bond and attachment of a nitro group to the resulting radicals (Eq. 132). In accordance with the free-radical nature of the reaction, small amounts of chlorine, which acts as



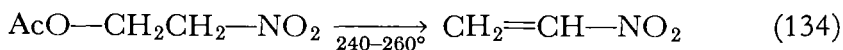
a radical generator, have a marked promoting effect.²⁸⁶

In addition to the foregoing several reactions by which a nitro group is formed or introduced into an organic compound, there are several reactions of synthetic importance involving conversion of an existing nitro compound into one of another type. The formation of β -aryl nitroalkanes by Friedel-Crafts alkylation with nitro olefins²⁸⁷ (Eq. 133) is an example. The formation of nitroalkanes by the selective reduction of

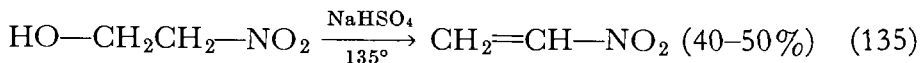


conjugated nitro olefins^{158, 165a} is of preparative significance because of the possibilities of preparing nitro olefins independently, particularly from β -hydroxy or β -acetoxy nitroalkanes, which are products, respectively, of the Henry reaction^{103, 104} and nitration of olefins with acetyl nitrate.^{234, 276} It is appropriate to describe methods for carrying out these conversions in this context.

Conjugated nitro olefins are generally prepared by the mild pyrolysis of β -acetoxy nitroalkanes^{88b, 288} even nitroethylene itself, a compound of quite limited stability, can be prepared in this way (Eq. 134). Similarly good results have been obtained with the dehydration of β -hydroxy



nitroalkanes by heating them with sodium bisulfate^{289, 290} (Eq. 135). β -Aryl β -hydroxy nitroalkanes, the initial products of the Henry reaction



of benzaldehydes with primary nitroalkanes, are so readily dehydrated that the nitro olefin is often formed spontaneously under the conditions of the condensation. Nitro olefins have also been prepared by the reverse Diels-Alder reaction with nitro-9,10-ethanoanthracenes.¹³⁹

The principal methods for preparing *gem*-dinitro compounds have already been mentioned in other connections; they are oxidative nitration

of mononitroalkanes,^{141, 142} the Ponzio reaction of oximes with nitrogen tetroxide,^{121, 291} and the ter Meer synthesis²⁹² (bromination of mononitroalkanes and displacement of the bromide with a nitrite salt). 1,1,1-Trinitro compounds are prepared either by nitration of 1,1-dinitro compounds¹²² or nitrolic acids¹⁴² or by condensation reactions of the Mannich or Michael type with nitroform.²⁹³ The preparation of *gem*-dinitro and 1,1,1-trinitro compounds has been reviewed elsewhere.²

Nitrolic acids are prepared by the nitrosation of primary nitroalkanes²⁹⁴ (usually by acidifying a solution of a nitronate salt and an alkali nitrite) or by the controlled reaction of nitrogen tetroxide with aldoximes.^{5, 121}

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chapter
fifteen

Esters and Amides of Nitrogen Oxy-acids

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NOMENCLATURE

Esters of hyponitrous, nitrous, and nitric acids are named in the normal way for esters in general by use of the name of the alkyl radical followed by the name of the inorganic anion. These compounds are indexed in *Chemical Abstracts* under their individual names, without inversion; i.e., ethyl nitrite is indexed under "E." Occasionally esters are met with that cannot be named in this way for lack of a suitable name for the organic moiety as an alkyl radical; in such cases the name of the corresponding alcohol (i.e., hydroxy compound) is used, as in "cellulose nitrate." An alternative having wide popular use for some common

explosives is based on the consideration that nitrate esters are O-nitro compounds; the locant O— is left understood, and the prefix “nitro-” is added to the name of the alcoholic substance, as in “nitroglycerine” and “nitrocellulose.” With complex polyfunctional compounds, this type of nomenclature with the locant O— explicitly given may be the only practical method, as in “2-O-nitro-3,5-dibenzoyl-D-arabinofuranosyl chloride.” In still other situations, the prefix forms nitroxy (nitrato) or nitrosoxy (nitrito) may become necessary.

Amides of nitrous acid bear the class name nitrosamines, and individual members are often named accordingly, as in “dimethylnitrosamine,” $(\text{CH}_3)_2\text{N}-\text{NO}$. *Chemical Abstracts* does not use the class name, but indexes individual compounds as N-nitroso derivatives under the name of the parent amine. Amides of nitric acid bear the class name nitramines, although the inorganic parent compound is called nitramide. Individual compounds are commonly named by use of -nitramine as a suffix, as in “methylethyl nitramine,” $\text{MeEtN}-\text{NO}_2$; *Chemical Abstracts* indexes them in the same way as nitrosamines, as N-nitro derivatives of the parent amines. The “esters” of the *aci*-nitro tautomers of monosubstituted nitramines are usually named in the original literature as

O,N-disubstituted nitramines, (e.g., $\text{CH}_3\text{N}^+=\text{N}(\text{OEt})-\text{O}^-$: O-ethyl-N-methylnitramine), but they have also been named as alkyl iminonitronates and as disubstituted isonitramines (the last name has unfortunately been sabotaged by the deplorable use of the term isonitramine in the early 20th century to mean N-nitrosohydroxylamines). *Chemical Abstracts* most confusingly lists some examples by names of the foregoing type, under “nitramide,” and some under the parent amine, as N-(alkyl-*aci*-nitro) derivatives, without cross-indexing. The analogous compounds derived from nitrosamines, $\text{R}-\text{N}=\text{N}-\text{OR}$, are usually referred to as alkyl diazotates, but might equally well be named as alkoxydiimides or as iso-

nitrosamine alkyl ethers. Their ternary salts, $\text{R}_2\text{N}^+=\text{NOR}$, have been called O-alkylnitrosimmonium salts, but might better be named O-alkylisonitrosammonium salts, to avoid confusion with derivatives of nitrosimines.

Nitroso and nitro derivatives of aldimines and ketimines are called nitrosimines ($\text{R}_2\text{C}=\text{N}-\text{NO}$) and nitrimines ($\text{R}_2\text{C}=\text{N}-\text{NO}_2$) (the prefix “pernitroso” was at one time used for nitrimines and isomeric compounds whose structure was uncertain). N-Nitro amides are always named by use of the nitro prefix; the confusing class name “nitramides” has unhappily been used for them occasionally. Nitroso and nitro derivatives of hydrazines, hydroxylamines, etc., are also named by the use of N-nitroso- or N-nitro-prefixes. The two isomeric alkylation products of an N-nitroso-N-alkylhydroxylamine are named N-nitroso-N-

alkoxyamines (or N-nitroso-O,N-dialkylhydroxylamines) and N-alkyl-N-alkoxydiimide N-oxides (variants of the latter name, some rather curious, have also been used).

There are altogether five structurally isomeric functions within the scope of this chapter corresponding to the formula $R_2N_2O_2$: hyponitrites, two types of O-alkyl derivative of N-nitrosohydroxylamine, and N,N- and O,N-dialkylnitramines. Examples of each are known as distinct, properly characterized compounds; geometrical isomers are in principle possible with three of the structural types. The dimers of C-nitroso compounds (Chapter 13) constitute a sixth isomeric structure type. The confusion in the meaning of the term "isonitramine" is apparently responsible for the fact that certain O,N-dialkylnitramines are incorrectly classified in the Beilstein supplements as N-nitroso-O,N-dialkylhydroxylamines. Furthermore, uncertainties about structures, only recently resolved, have given rise to incorrect assignment of names (e.g., N-aryl-N'-alkoxydiimide N-oxides have been described and indexed as N-aryl-N'-alkyldiimide dioxides, whose structure is in fact now assigned to the dimers of nitroso compounds).

PROPERTIES

Our knowledge of hyponitrite esters is essentially confined to ethyl and benzyl hyponitrites.^{1, 2} The former is an oil, too unstable to distill even in vacuum, insoluble in water, soluble in alcohol, ether, or benzene. The neat liquid explodes when warmed above 80°. Benzyl hyponitrite is a colorless, crystalline solid, mp 48–49°. The dipole moments (1.4 D for ethyl, 0.4 D for benzyl) are believed to be most consistent with a *trans* configuration about the N—N double bond, in which free rotation about the O—N bond accounts for the values observed. The gross structure of alkyl hyponitrites as O-alkyl compounds, $R-O-N=N-O-R$, is established by the fact that reduction gives only alcohol and no amine.¹

The simple alkyl nitrites and nitrates are sweet-smelling, volatile, colorless substances, insoluble in water but miscible with the common organic solvents. Methyl and ethyl nitrites are gases (bp -17° and 18°) and illustrate the generalization that nitrites are markedly more volatile than the hydrocarbons of closest molecular weight (cf. *n*-pentane, bp 36°). The contrast in boiling points with the isomeric nitroalkanes is great (cf. nitromethane, bp 101°). Secondary and tertiary alkyl nitrites, such as *tert*-butyl nitrite,³ bp $34^\circ/250$ mm., are well known. Alkyl nitrites decompose slowly at room temperature, but can be stored for weeks in a refrigerator; distillation conducted much above room temperature is very frequently accompanied by some decomposition.

The simple alkyl nitrates, such as methyl (mp -83° , bp 64.6°), ethyl (mp -112° , bp 88°) and *tert*-butyl (mp -34° , bp $28^{\circ}/4$ mm.) are much less volatile than the corresponding nitrites, and, in fact, boil a little higher than the alcohols having the same number of carbons and distinctly higher than the saturated hydrocarbons of similar molecular weight (cf. isohexane, bp 60.3° , vs. ethyl nitrate, bp 88°). Glyceryl nitrate (nitroglycerine) melts at 8° . Azeotropes of the alkyl nitrates with water or alcohols are common. Although alkyl nitrates are stable to storage when quite pure, traces of acids or oxides of nitrogen sensitize them to decomposition and may cause explosion on heating or storing at room temperature. When pure, alkyl nitrates are stabler to distillation than the nitrites, but even so, temperatures above 110° are to be avoided.

Few acyl nitrites are known; one of the simplest, trifluoroacetyl nitrite ⁴ (more properly considered as nitrous trifluoroacetic anhydride) is an amber liquid, bp $45^{\circ}/80$ mm., and tetrafluorosuccinoyl nitrite ⁴ is a yellow, crystalline solid, mp $44-48^{\circ}$. Acyl nitrates are in general liquids, not very stable neat, but more stable in solution in acetonitrile. Acetyl nitrate has been distilled at $22^{\circ}/77$ mm., and benzoyl nitrate has been obtained as a yellow oil. A liquid, bp 128° , originally described as "diacetyl orthonitric acid," ⁵ $(\text{AcO})_2\text{NO}_2\text{H}$, could hardly be so volatile with such a structure and presumably was actually impure acetyl nitrate.

Thiolnitrites, $\text{R}-\text{S}-\text{NO}$, are red liquids having a green reflection, or green solids; ethyl thiolnitrite distills at $19^{\circ}/85$ mm. They decompose very easily on heating or exposure to air.

The dialkylnitrosamines are much less volatile than the nitrite esters, but much more soluble in water; dimethylnitrosamine, for example, boils at 154° and is miscible with water (potassium carbonate salts it out). They are yellowish liquids or low-melting solids, much more stable than alkyl nitrites, and can be stored for weeks or more. Monosubstituted nitrosamines, however, are highly unstable; methylnitrosamine and phenylnitrosamine are known as solids isolable only at subzero temperatures.⁶ A few primary nitrosamines of complex structure, such as certain tetrazolyl and triazolyl nitrosamines,⁷ can nevertheless be isolated as crystalline solids stable at room temperature.

Although it has not been established whether primary nitrosamines have the tautomeric isonitroso structures, $\text{R}-\text{N}=\text{N}-\text{OH}$ (also known as diazohydroxides), alkyl ethers of the type $\text{Ar}-\text{N}=\text{N}-\text{O}-\text{R}$ are known.⁸ Benzenediazo methyl ether (O-methylisonitrosoaniline) is a somewhat volatile oil with a pungent odor, insoluble in water, but soluble in the usual organic solvents.^{9a} It is quite unstable and may explode on standing; its *p*-nitro derivative,^{8b} straw-colored needles, mp 83° , is more stable. Benzenediazo *p*-nitrophenyl ether has been obtained as a solid that decomposes spontaneously shortly after isolation.^{9b}

Substances believed to be nitrosimines, $\text{Ar}_2\text{C}=\text{N}-\text{NO}$, have been obtained as purple oils from the treatment of benzophenone imines with nitrogen tetroxide in the presence of sodium acetate.¹⁰

Nitroso derivatives of hydroxylamines are known in some variety¹¹; the N-aryl members, such as N-phenyl-N-nitrosohydroxylamine ("Cupferon"), mp 59°, are generally solids of moderate to low stability, more stable in the form of salts. N-Methyl- and N-ethyl-N-nitrosohydroxylamine are known in aqueous solution; they have biting odors and are evidently somewhat volatile. The completely alkylated N-nitrosohydroxylamines,¹² such as the O,N-dimethyl derivative, a yellow oil that distills at 60°/30 mm. and explodes above 200°, are more stable. Nitrosohydroxylamine also gives rise to another series of disubstituted derivatives, alkoxy substituted azoxy compounds,¹³ such as N-methyl-N'-methoxydiimide N-oxide, $\text{CH}_3\text{O}-\text{N}=\text{N}^+(\text{CH}_3)\text{O}^-$, a colorless volatile oil, and N-phenyl-N'-methoxydiimide N-oxide, mp 40°.

Nitroso hydrazines, also of generally limited stability, are known with one, two, or three aryl and/or alkyl substituents (cf. Chapter 9). Trimethylnitrosohydrazine,^{14a} bp 42°/10 mm., mp -7°, is miscible with water, and slowly decomposes on standing; N-methyl-N-nitrosohydrazine,^{14b} mp 45°, is very soluble in water, difficultly soluble in ether, and somewhat volatile; N,N'-dimethyl-N-nitrosohydrazine^{14b} is a yellow oil, bp 56°/10 mm., that deflagrates on heating and is miscible with water and organic solvents other than petroleum ether.

N-Nitroso derivatives of monosubstituted amides are known in assorted types; most of them are solids, such as N-methyl-N-nitrosoacetamide, mp -8.5°, bp 116°, and are of variable but seldom very great stability. Exceptional ones, such as N-nitroso-N-methylurea and N,N'-dinitroso-N,N-dimethylterephthalamide, may be stable to prolonged storage. N-Nitrosoacetanilide, mp 51°, is a frequently employed arylating agent. A very few N-nitroso derivatives of unsubstituted amides have been isolated, such as N-nitrosourethan, yellow needles, mp 51-52° dec.

The nitramines are generally low-melting solids or liquids, such as: $(\text{CH}_3)_2\text{N}-\text{NO}_2$, mp 58°, bp 187°; $\text{CH}_3\text{NH}-\text{NO}_2$, mp 38°; $\text{ONH}-\text{NO}_2$, mp 46°; $\text{Et}_2\text{N}-\text{NO}_2$, bp 207°. The smaller members are easily soluble in water; even isoamyl nitramine can be recrystallized from hot water. The simple O,N-dialkyl *aci*-nitramines, such as $\text{CH}_3\text{N}=\text{NO}_2\text{CH}_3$, bp 112°, are liquids of much lower boiling point than their nitro isomers; geometrically isomeric forms have been recognized, but have not been completely separated.¹⁵ N-Nitro derivatives of both substituted and unsubstituted amides are known in rather limited number; they are generally stable, colorless, low-melting solids, such as nitrourea, mp 159° dec., nitrourethan, mp 64°, and N-methyl-N-nitrourethan, mp 8°, bp 98-99°/20 mm. Nitrimines, $\text{R}_2\text{C}=\text{N}-\text{NO}_2$, are generally stable,

colorless, liquids or low-melting solids, insoluble in water, but soluble in organic solvents; pinacolone nitrimine distills at 81–83°/10 mm. and camphor nitrimine melts at 43°.

N-Nitro hydroxylamines are apparently unstable toward conversion to oximes by elimination of nitrous acid, for attempts to prepare them by alkylation of the sodium salt of nitrohydroxylamine or alkaline nitration of N-alkylhydroxylamines with ethyl nitrate have failed.^{16a} Similar attempts to prepare a nitrohydrazine by alkaline nitration of phenylhydrazine produced phenyl azide, azobenzene, nitrobenzene, aniline, biphenyl, and benzene, but nothing identifiable as a primary product of N-nitration.^{16b}

Esters of nitrogen oxy acids are neither acidic nor basic in the ordinary sense. Primary nitrosamines are apparently distinctly acid, in view of the stability of the diazotate anions, ArN_2O^- (cf. Chapter 11), but practical difficulties have prevented the quantitative elucidation of the interrelationships between the tautomeric nitrosamine-isonitrosamine equilibrium and the separate acidity constants. Nitrosourethan is apparently a stronger acid than acetic acid. Secondary nitrosamines are basic enough to form salt-like addition products with strong acids in non-aqueous media, but such substances are broken up into their components by water.¹⁷ Nitroso hydroxylamines having an unsubstituted hydroxyl group are acidic, as is to be anticipated in view of their relationship to the hydroxamic acids, and even form salts with bases as weak as ammonia; N-nitroso-N-phenyl-hydroxylamine^{18a} has $pK_a = 4.42$ and the benzyl analog,^{18b} pK_a 5.19.

Primary nitramines, like the parent compound, are weak acids; methyl nitramine¹⁹ has $pK_a = 6.14$ and phenyl nitramine,^{19b} pK_a 3.75. Nitramines, unlike the nitroalkanes, behave as normal acids.²⁰ Nitrimines with α -hydrogens are very weakly acidic, forming salts with alcoholic alkali and in some instances reportedly dissolving in strong aqueous alkali, from which they can be recovered unchanged on acidification.²¹ Nitrourea and nitrourethan (pK_a 3.32) are strongly acidic.

The molecular structure of methyl nitrite and nitrate have been examined by electron diffraction.²² The C—O distances, 1.44 Å, are normal; the single-bond O—N distances are almost the same in both compounds (1.37 Å). The terminal N—O bond seems to be a trifle shorter ($1.22 \pm .02$ Å) in the nitrite than in the nitrate ($1.26 \pm .05$ Å). In both compounds there is an obtuse C—O—N angle (nitrite, 109.5°; nitrate, $105 \pm 5^\circ$), which in the nitrite is essentially the same as the O—N—O angle; in other words, the carbon and the terminal oxygen are staggered with respect to the O—N axis.

Nitrosamines have been neglected by both electron and X-ray diffractionists, but the salt of a nitrosohydroxylamine, Traube's salt,

$\text{CH}_2(\text{N}_2\text{O}_2\text{K})_2$, has been examined.²³ Both N—O distances are shorter than ordinary single bonds, and the N—N distance is midway between the single- and double-bond distances.

Dimethylnitramine ^{24a,b} and ethylenedinitramine ^{24c} and its sodium salt ^{24d} have been investigated crystallographically. The nitramine moieties are planar, with a C—N—N angle distinctly larger than the tetrahedral, very short N—N distances (1.26–1.33 Å), and N—O distances similar to those in methyl nitrate. Presumably the short N—N distances result in markedly restricted rotation about the N—N bond.

The dipole moments of several nitramines and nitrosamines have been determined.²⁵ Those of nitramines (4.6 to 4.9 D) are somewhat larger than those of nitrosamines (3.98 to 4.32 D). Methyl nitrate, whose dipole moment has been determined ²⁵ to be 2.85 D, is a solvent of considerable ionizing power and dissolves many salts; values of 2.2–2.3 D have been reported for the dipole moment of the simple alkyl nitrites.

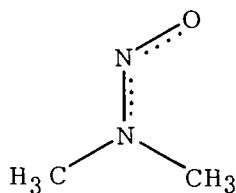
The ultraviolet spectra of nitrites ^{27–30} and of nitrosamines ²⁷ are similar to those of C-nitroso compounds; absorption is continuous from about 400 mμ to shorter wavelengths, with a low-intensity maximum near 360 mμ (generally 340–385 mμ) due to an $n \rightarrow \pi^*$ transition and a moderately intense maximum ($\epsilon \sim 7000$) due to a $\pi \rightarrow \pi^*$ transition, near 220 mμ for dialkyl nitrosamines, shorter for alkyl nitrites. The short-wave absorption of nitrosamines is shifted to longer wavelengths by conjugation, as in N-methyl-N-nitrosoaniline, λ_{max} 274 mμ; bulky substituents on nitrogen, which force the nitroso group out of the most effective orientation for π -orbital overlap, cause a shortening (e.g., N-isopropyl-N-nitrosoaniline, λ_{max} 250 mμ). The long-wave absorption of nitrosamines is quite sensitive to solvent effects, a characteristic that can be made use of in identification. N-Nitrosohydroxylamines lack this long-wave band, and their spectra more closely resemble those of nitramines.²⁸ The dimethyl derivative N-methyl-N'-methoxydiimide N-oxide has $\lambda_{\text{max}} = 238 \text{ m}\mu$.¹²

Nitramines have ultraviolet spectra ^{28, 31} very similar to those of nitrosamines, except for the lack of the weak, long wavelength band; absorption is continuous down from about 320 mμ, with a maximum at 225–250 mμ, $\epsilon \sim 5500$ for secondary nitramines, ~ 7000 for primary. Conversion of primary nitramines to their anions results in only a slight shift to longer wavelengths. Nitrourethans ³² absorb at about 5 mμ longer than the corresponding nitramines, but nitrimines ²⁰ are distinctly different, having absorption near 270 mμ and much weaker. O,N-Dialkyl *aci*-nitramines ¹⁵ absorb between 205 and 217 mμ. Alkyl nitrates ²⁸ absorb continuously down from about 310 mμ, with an inflection near 260 mμ, and generally resemble nitroalkanes.

The infrared spectra of nitrosamines ^{25, 27} show characteristic strong

bands at 1421–1441, 1352–1367, and 1266–1290 cm^{-1} , in addition to other strong bands. The high-frequency band, clearly due to $\text{N}=\text{O}$ stretching, significantly comes at a distinctly lower frequency than that of alkyl nitrites ^{27, 33} (near 1660 cm^{-1}), and indicates an appreciable degree of conjugation with the amine nitrogen. The nitrites actually show a doublet, which has been tentatively attributed to *cis* and *trans* configurations. Secondary nitramines show ²⁵ the asymmetric and symmetric stretching frequencies of the nitro group at 1504–1529 and 1274–1304 cm^{-1} , respectively, somewhat lower in the first instance than those of primary nitramines ³⁴ and alkyl nitrates ³³ (those of the latter fall at 1625–1655 and 1270–1285 cm^{-1}). Nitrimines ²⁰ have the nitro bands at 1560–1570 and 1310–1320 cm^{-1} , and show $\text{C}=\text{N}$ stretching at 1620–1640 cm^{-1} . The O,N-dialkyl nitramines,¹⁵ which do not have a nitro group, resemble azoxy compounds and have bands at 1544–1564, 1232–1252, and 897–707 cm^{-1} .

Reference has already been made to restricted rotation about and shortening of the $\text{N}-\text{N}$ bond in nitrosamines and evidence for marked conjugation between the nitroso group and the unshared electron pair on the amine nitrogen. The most persuasive evidence for these phenomena is found in the nuclear magnetic resonance spectra.^{30, 31, 35} Dimethylnitrosamine, for example, gives two equally intense signals at 25°, separated by 26 cps at 40 Mc; the separation becomes less as the temperature is raised and disappears entirely at about 180°. These observations can be accounted for if it is assumed that the molecule is fixed in a planar configuration with an energy barrier of about 23 kcal/mole; the two methyl groups experience the asymmetrically oriented nitroso group differently and thus resonate at different field strength. Unsymmetrically



$$\tau = 6.24 \qquad \tau = 7.04$$

(n.m.r. consequences of fixed geometry
in dimethylnitrosamine)

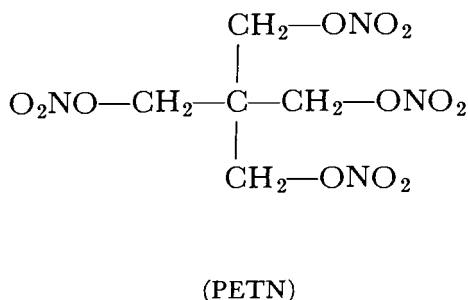
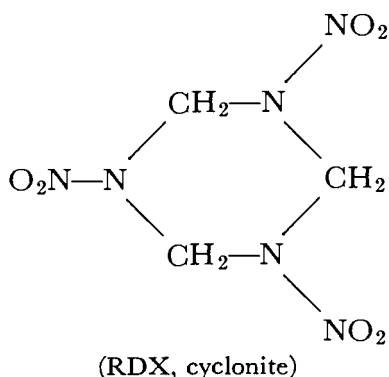
substituted nitrosamines, of course, have unequal equilibrium concentrations of the two geometrical isomers then possible; in some, such as methyl-*tert*-butylnitrosamine and N-methyl-N-nitrosoaniline, only the *cis*-methyl form is present.³⁰ Restricted rotation would also be expected in nitramines, but the symmetry of the nitro group would not lead to

the existence of geometrical isomers or of differentiated NMR signals. Hindered rotation in alkyl nitrites has also been detected by NMR.³⁶

Parachor, molecular refraction, and polarization data about nitrites, nitrates, nitrosamines, and nitramines have been tabulated.^{25, 37}

The enthalpies of formation³⁸ of the N-nitro group (265 kcal/mole) and the O-nitro group (270 kcal/mole) differ only a little from that of the C-nitro group (283 kcal/mole). It is thus not surprising that the greatest importance of nitrates and nitramines lies in the field of explosives and propellants,³⁹ a subject too large and too applied to be reviewed here. The energy content that is the basis of the explosive properties is a result of the high energy of oxygen-nitrogen bonds compared to oxygen-carbon, oxygen-hydrogen, and nitrogen-nitrogen bonds; the difference in energy is released when compounds containing N-bound oxygen decompose so as to form water, carbon monoxide or dioxide, and nitrogen. The energy per mole obtainable by such decomposition is at a maximum when the ratio of oxygen to carbon and hydrogen in the molecule is exactly that required for the conversion of all carbon to carbon dioxide and all hydrogen to water with nothing but nitrogen left over; such a condition is known as zero oxygen balance. Commercial and military explosives come close to zero oxygen balance, but for various practical reasons the known compounds having exactly zero oxygen balance, such as ethylene dinitrate, are not generally used. In the interests of safety, all compounds with a low oxygen balance should be treated as potentially explosive, and it should be borne in mind that most of the smaller nitrates and nitramines may explode when heated to 200°.

The requirements for a useful explosive or propellant are not only high energy content, but stability to storage, adequate but not excessive sensitivity, lack of phase change in the ordinary climatic range of temperatures, and cheapness. For propellants, a controllable rate of decomposition ("burning") and a high volume of gas production are also important. Apart from the C-nitro compounds mentioned in Chapter 14, among the most widely used substances satisfying the requirements are: glyceryl nitrate (nitroglycerine), the principal active constituent of dynamite, invented by Alfred Nobel in 1863; nitrocellulose ("guncotton"), which for use as an explosive must have a high fraction of the available hydroxyl groups nitrated; trinitrophenylmethylnitramine (Tetryl); trimethylene trinitramine (RDX, cyclonite); and pentaerythrityl tetranitrate (PETN). Mixtures of these with each other or with other substances may be compounded to achieve desirable properties; "blasting gelatine," a gelatinous solution of nitrocellulose in nitroglycerine, is an example. Inhibitors are usually added to enhance stability to storage; these are substances such as diphenylamine that remove oxides of nitrogen, which catalyze decomposition.



Nitrocellulose with a low degree of nitration is less explosive (although it is highly inflammable) and has seen extensive use in the manufacture of photographic film and celluloid.

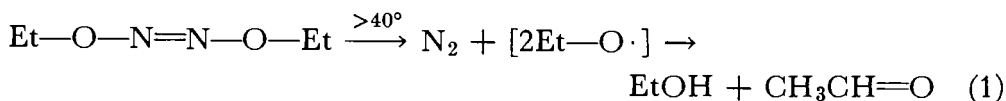
The physiological properties of alkyl nitrates^{40, 41} and nitrites are not insignificant. Alkyl nitrates strongly affect the circulatory system and act as vasodilators. In controlled doses, alkyl nitrates and nitrites have therapeutic application (e.g., ethyl nitrite, known as "sweet spirits of nitre"), but heavy exposure is definitely toxic. These compounds may be absorbed through the skin as well as by inhalation. Alkyl nitrites accelerate the heartbeat. Nitrosamines, particularly dimethylnitrosamine, are toxic and reported to be carcinogenic. N-Nitroso amides are irritating in various degrees, and many of the N-alkyl-N-nitrosourethans cause severe rashes and attack the eyes; N-methyl-N-nitrosourethan, moreover, is carcinogenic.

Naturally occurring oxygenated nitrogen compounds are exceptional, but among them is a nitrosamine, N-nitroso-*p*-methylaminobenzaldehyde, isolated from cultures of *Clitocybe suaveolens*.⁴²

REACTIONS

A. Hyponitrites

Relatively little is known of the chemistry of the alkyl hyponitrites; most of the attention paid to them has been concerned with their easy decomposition. But little warming above room temperature is required to cause rapid decomposition^{43a} to nitrogen and a mixture of alcohol and aldehyde corresponding formally to disproportionation of alkoxyl radicals (Eq. 1).² The formation of free radicals in hyponitrite decomposition

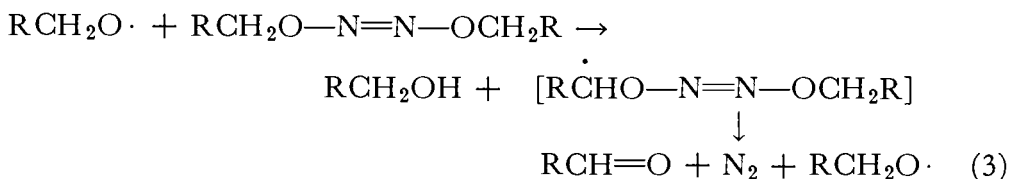


has been established by demonstrating that polymerization of vinyl monomers is initiated with an effectiveness greatly exceeding that of

benzoyl peroxide.^{43b} Decomposition is autocatalytic unless a high concentration of a free-radical trap, such as quinone, is present. Since alkoxy radicals,⁴⁴ $\text{RCH}_2\text{O}\cdot$, can cleave into an alkyl radical and formaldehyde, abstract hydrogen from the solvent (Eq. 2), or take part in a chain reaction leading to apparent disproportionation products (Eq. 3),



one might expect decomposition in high dilution to favor products arising



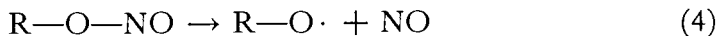
only from cleavage or reduction at the expense of the presumed disproportionation. The fact, however, that the products corresponding to disproportionation cannot be reduced to less than 50% of the theoretical amount has been taken to indicate that much disproportionation takes place inside the solvent cage in which each pair of alkoxy radicals is generated. The efficiency of production of radicals available for other reactions is thus only about 50%.

Reduction of alkyl hyponitrites by various metals produces only the parent alcohol and no amine.¹

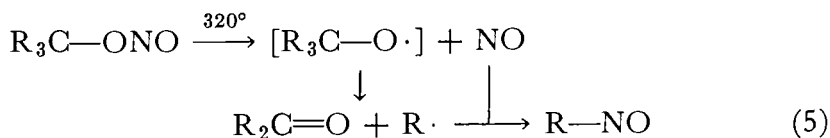
B. Nitrites

The chemistry of the alkyl nitrites is dominated by their heat- or light-induced decomposition reactions and by action as nitrosating agents.

HEAT Although there exists a claim⁴⁵ that heating causes isomerization of ethyl nitrite to nitroethane, it has never been substantiated. On the other hand, there is a large body of experimental evidence that other products are formed instead and are best accounted for by the assumption that the initial step is homolytic cleavage of the $\text{RO}-\text{N}$ bond (Eq. 4).⁴⁶



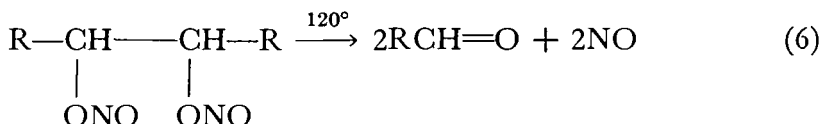
Tertiary alkyl nitrites give significant yields of ketone and nitrosoalkane if a flow system is used so that the nitroso compound can be removed quickly from the reaction zone and quenched⁴⁷ (Eq. 5). When unsym-



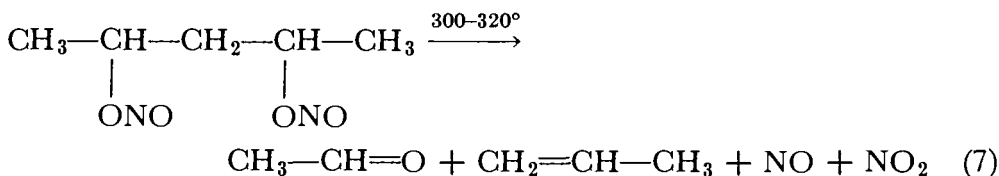
metrical tertiary alkyl groups are involved, the predominant nitroso product is that derived from the largest available alkyl group; i.e., the

alkyl radical cleaves to give the most stable alkyl radical when there is a choice. The fact that formation of $R\text{—NO}$ competes with dimerization of $R\cdot$ to $R\text{—}R$ with unanticipated efficiency suggests that the overall process may be in part concerted. An interesting case, in which all parts are found attached together in the product, is the pyrolysis of cyclohexyl nitrite,⁴⁴ which gives 6-nitrosohexanol. A major competing reaction, which may, indeed, become the principal reaction in the liquid phase at lower temperatures, is formation of the disproportionation products of alkoxyl radicals^{41, 46} (alcohol and aldehyde or ketone). It has been shown that the 2-octanol formed when *d*-2-octyl nitrite is decomposed at 100° is optically pure,⁴⁸ thus further demonstrating that cleavage of the $RO\text{—}N$ rather than the $R\text{—}O$ bond is involved.

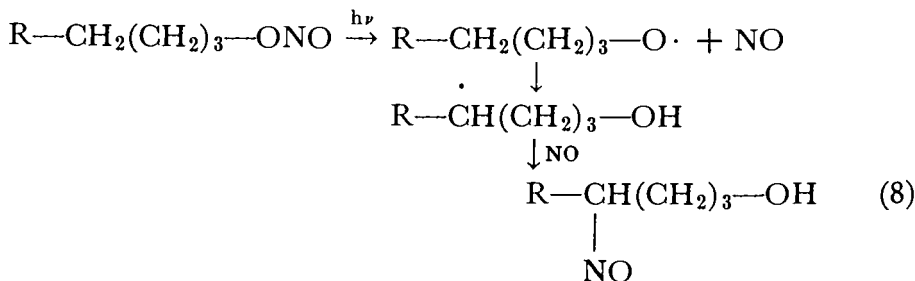
With vicinal dinitrites, carbon-carbon cleavage is a significant feature^{44, 49}; the process resembles the oxidative cleavage of vicinal glycols by periodate (Eq. 6), but it is not as efficient, and α -diketones and glycols



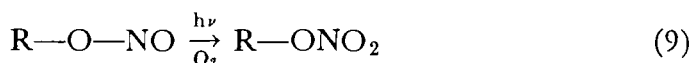
are also formed. 1-3-Dinitrites also undergo carbon-carbon cleavage on heating and give an olefin and an aldehyde (or ketone) (Eq. 7).^{49b}



PHOTOLYSIS The photolysis⁵⁰ of alkyl nitrites, which has been studied mostly in solution, is similar in the overall pattern to pyrolysis, but there are some significant differences. Alkoxyl radicals are initially formed and undergo the expected reactions of disproportionation, cleavage (Eqs. 4 and 5), and hydrogen abstraction from the solvent; however, when the alkyl chain is at least four carbon atoms long, the Barton reaction, which gives rise to 4-nitroso alcohols, comes into play.⁵¹ This reaction is evidently a case of “backbiting” by the alkoxyl radical to form the isomeric 4-hydroxyalkyl radical, which then combines with nitric oxide (Eq. 8). The

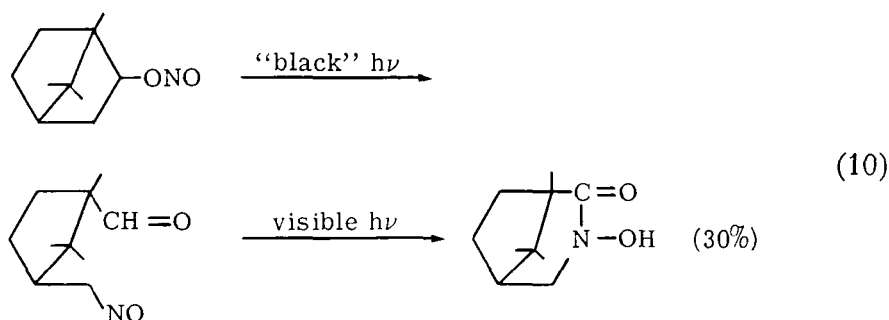


yields of nitroso alcohols, which are actually obtained in the form of their dimers, are not generally high, but in favorable cases may be of appreciable preparative value. They obviously depend on the extent to which the aforementioned competing reactions incur and are a function not only of structure, but also of experimental conditions.^{51, 52} Solvents that are at the same time poor hydrogen donors and poor traps for radicals, such as benzene, give the best results in the Barton reaction. In the presence of oxygen, reaction is diverted largely to the formation of alkyl nitrate (Eq. 9).⁵³ This reaction owes its success to the fact that alkyl



nitrates, unlike the nitrites, do not absorb radiation of wavelength above 310 m μ and are thus not dissociated.

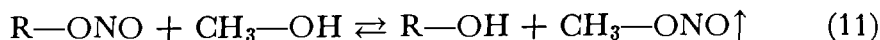
Cycloalkyl nitrites may give Barton-reaction products (4-nitroso-cycloalkanols) if backbiting is stereochemically feasible, hydrogen-abstraction products (cycloalkanols), or may undergo ring opening to give ω -nitroso aldehydes (Eq. 10); the latter may undergo recyclization to form



hydroxamic acids if visible light is used along with the ultraviolet.⁵⁴

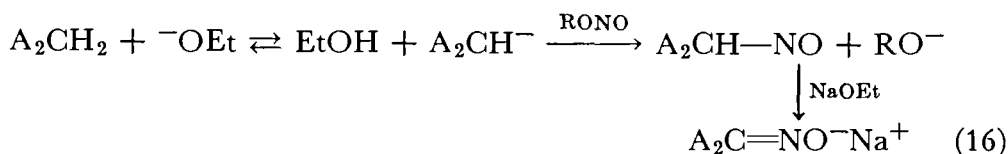
The Barton reaction has been demonstrated⁵⁵ not to be a chain process; the quantum yield is considerably less than 1. Differences between the vapor-phase photolysis reaction and pyrolysis or liquid-phase photolysis have been attributed to formation of alkoxyl radicals in an excited state in vapor-phase photolysis.⁵⁶

HYDROLYSIS AND SOLVOLYSIS The solvolysis of alkyl nitrites in water or alcohols is fairly rapid in neutral solution and is accelerated markedly by acids, but little by bases. Solvolysis in alcohols, i.e., transesterification, occurs so easily as to be of preparative value for the more volatile nitrites (Eq. 11). With hydrogen chloride, equilibration with nitrosyl

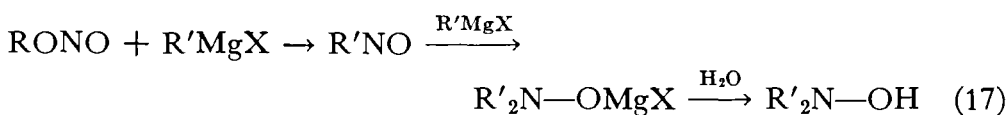


chloride and alcohol takes place⁵⁷ (Eq. 12).

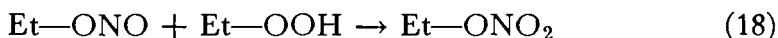




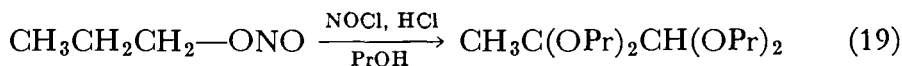
base as catalyst, such as sodamide, even relatively inactive methylene compounds, such as allylbenzene and alkylpyridines, can be thus nitrosated.⁶³ Organometallic reagents constitute the limiting case; a second mole of reagent attacks the presumed intermediate nitroso compound, giving the salt of a dialkylhydroxylamine^{64, 65} (Eq. 17).



OXIDATION Alkyl nitrites should in principle be oxidizable to alkyl nitrates, but the only reports of such a reaction appears to be those of oxidation of ethyl nitrite by ethyl hydroperoxide⁶⁰ (Eq. 18) and the photolytic oxidation⁵³ previously referred to. Hydrogen peroxide

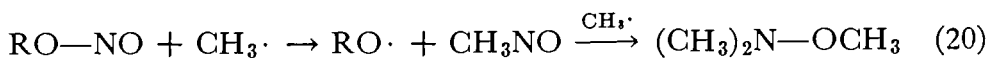


hydrolyzes the nitrite as well, converting it to alcohol and nitric acid. Oxidation at the β -carbon by alcoholic nitrosyl chloride appears to be a general reaction⁶⁶; acetals of 1,2-dicarbonyl compounds are produced (Eq. 19).



REDUCTION Alkyl nitrites are easily reduced to the corresponding alcohol, although it is not in all instances clear whether reduction precedes solvolytic cleavage of the O—N bond. Catalytic hydrogenation (Ni, 100–130°) of ethyl nitrite has been reported^{46a} to give some ethylamine in addition to ethanol and ammonia; at higher temperatures, ethanol disappears, and the products are mono-, di-, and triethylamine, and, above 300°, acetonitrile.⁶⁷ The formation of these nitrogenous products may arise from interaction of ethanol and ammonia in the presence of the surface catalyst. Lithium aluminum hydride⁶⁸ and hydrazine in the presence of a platinum or palladium catalyst⁶⁹ reduce nitrites to alcohols in high yield.

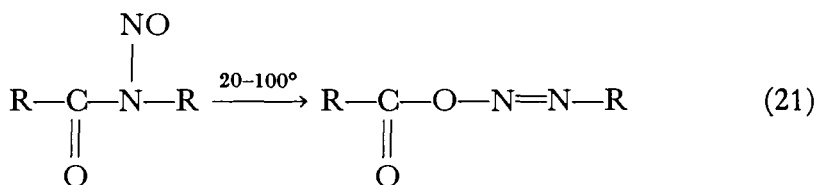
FREE RADICALS Alkyl nitrites, like C-nitroso compounds, are reactive toward free radicals. Methyl radicals, derived from di-*tert*-butyl peroxide or diacetyl peroxide, convert nitrites first to nitrosomethane,⁷⁰ which may itself react with more methyl radicals (Eq. 20). The isotope exchange



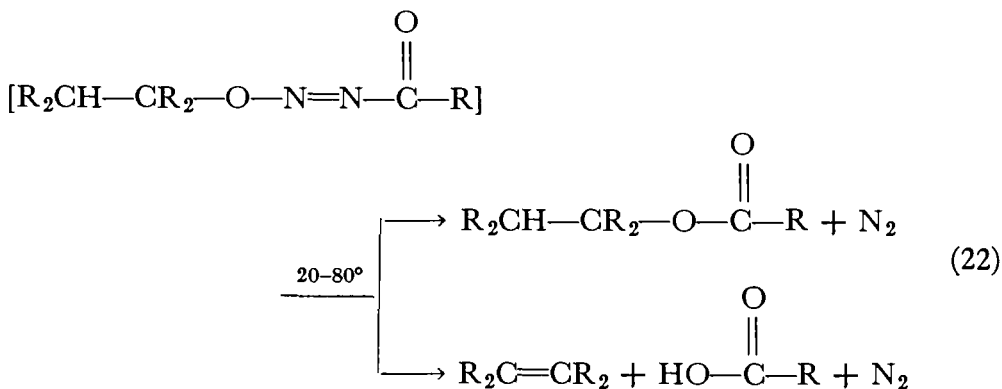
reaction between $\text{RO}-^{15}\text{NO}$ and nitric oxide may also be considered to be an example of free-radical attack.⁷¹

C. *N*-Nitroso Compounds

HEAT AND LIGHT Secondary nitrosamines are so very much more stable to heat than are alkyl nitrites that thermolysis is not an important reaction. Pyrolysis at 335° has been reported to give secondary amine and *N*-alkyl aldimine, the expected disproportionation products of dialkyl-amino radicals that would be formed by cleavage of nitric oxide from the nitrosamine.⁷² *N*-nitroso amides, however, are heat-labile substances; branching at either α -carbon lowers the decomposition temperature, which may fall even below room temperature; straight-chain *N*-alkyl-*N*-nitroso amides, however, may be stable to above 100° . The initial step appears to be rearrangement to a diazo ester by migration of the acyl group from *N* to *O* (Eq. 21)⁷³; these unstable intermediates are not



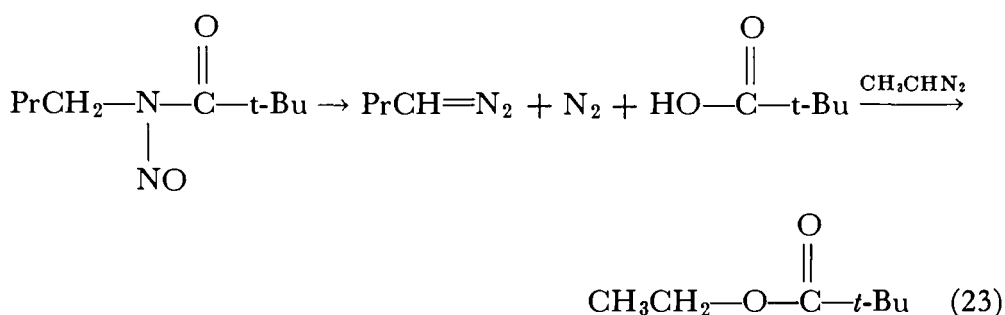
isolated, however. Those bearing an aryl group or nitrogen break up homolytically to give aryl radicals, as is discussed in connection with diazonium compounds in Chapter 11. *N*-Alkyl *N*-nitroso amides decompose by two paths, to give either an ester or an acid and olefin⁷⁴ (Eq. 22). When the *N*-alkyl groups are primary, the ester-forming reaction is the



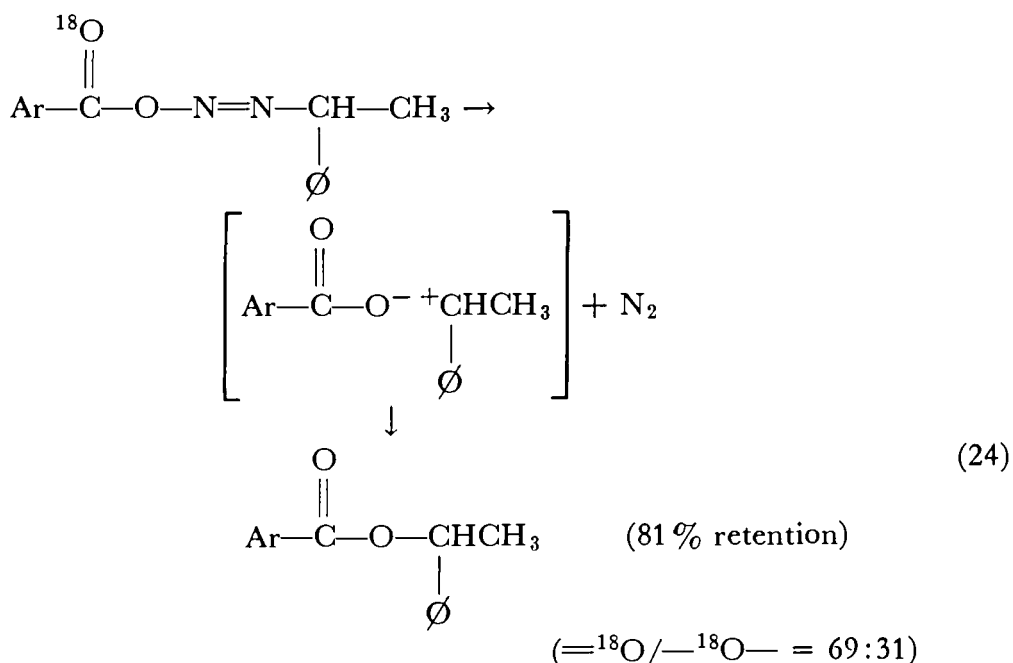
most important and may give as much as 84% of the product; it is also favored by lower temperatures and by nonpolar solvents.

The path by which esters are formed from nitroso amides evidently differs for primary *N*-alkyl compounds on the one hand and secondary and tertiary on the other. It has been demonstrated that primary *N*-alkyl nitroso amides break up initially to a diazoalkane and carboxylic

acid, which subsequently react rapidly to form the observed ester ⁷⁵; when *N-n*-butyl-*N*-nitrosopivalamide is allowed to decompose in the presence of an excess of diazoethane, the diazobutane formed is not entirely consumed by reaction with acid, and can be isolated (Eq. 23). Furthermore, when a nitroso amide in which the carbonyl oxygen is



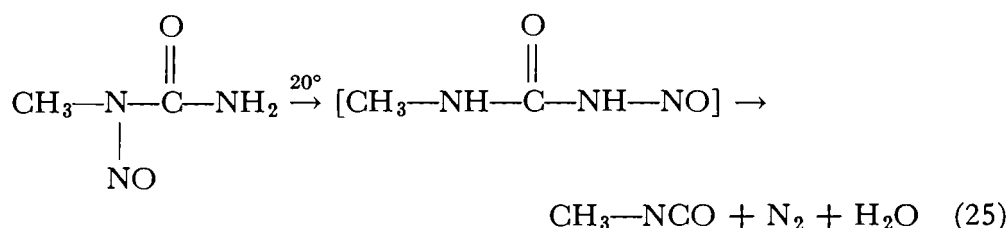
isotopically enriched is decomposed, the enrichment is found equally distributed between the two oxygens of the ester. Secondary *N*-alkyl nitroso amides, on the other hand, give rise to esters in which the carbonyl group still holds about two-thirds of the enrichment, and when the alkyl group has an optically asymmetric α -carbon, the alcohol isolated from the ester is largely of retained configuration. Nitroso amides of this type are believed to go to esters by an intramolecular path involving formation of a carbonium ion and carboxylate anion in the same solvent cage ⁷⁵ (Eq. 24), which collapse to the ester before more than a limited



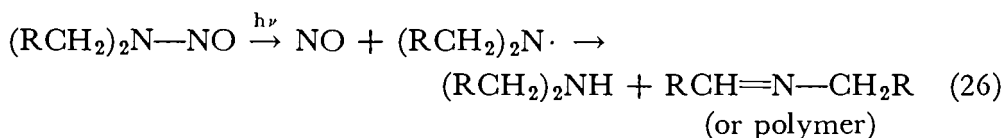
amount of rotation can take place.

N-Nitroso amides in which the N-alkyl group bears an α -carboalkoxy group are exceptional; not only do they decompose according to the same path as the primary alkyl analogs, but the diazo compounds formed do not react further and can be isolated.⁷⁴

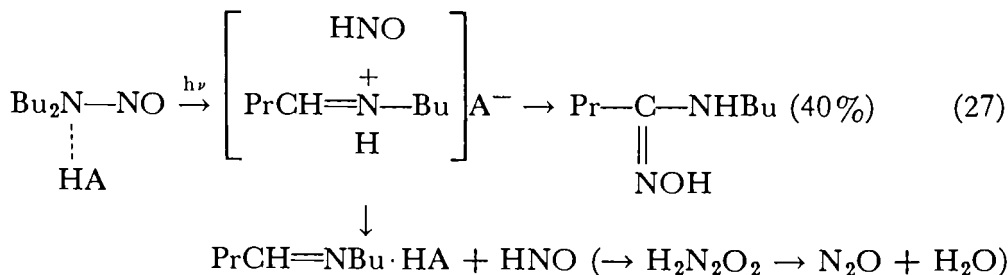
N-Nitroso lactams, which are very reactive, give rise to ω -hydroxy acids, or, when decomposed in alcoholic solution, to ω -alkoxy acids.^{76a} N-Nitroso sulfonamides decompose in a manner analogous to nitroso carboxamides. N-Nitroso-N-methylurea decomposes slowly on storage at room temperature, rapidly at 30°, to methyl isocyanate, nitrogen, and water.^{76b} These products suggest that the initial step is transnitrosation to the isomeric N-methyl-N'-nitrosoarea (Eq. 25).



Photolysis of nitrosamines has not received the attention that alkyl nitrites have. In the liquid phase, nitrosamines are relatively inert to photolysis in the absence of strong acids, but vapor-phase photolysis gives nitric oxide and products to be expected from disproportionation of dialkylamino radicals (Eq. 26).^{71, 77} In the presence of strong acids,

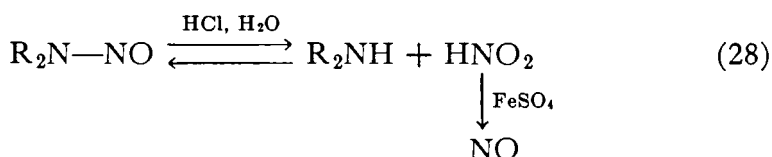


however, the reaction is greatly altered; the principal products are then amidoximes, accompanied by lesser amounts of aldehyde and amine.^{71, 77} It has been suggested that the initial step is cleavage of a hydrogen-bonded complex between acid and nitrosamine to form nitroxyl and an aldimine, which may either collapse within the solvent cage to form the amidoxime, or become separated to give rise to aldimine or its hydrolysis

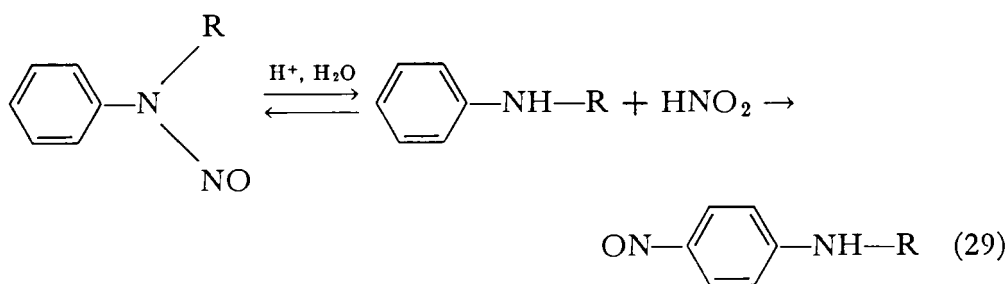


products and nitroxyl (Eq. 27), which dimerizes to hyponitrous acid, which has, indeed, been detected. Significantly, the ratio of amidoxime to aldimine is sensitive to both temperature and solvent. In 9 M sulfuric acid, where the nitrosamine is actually converted to its conjugate acid, amidoximes are not formed.

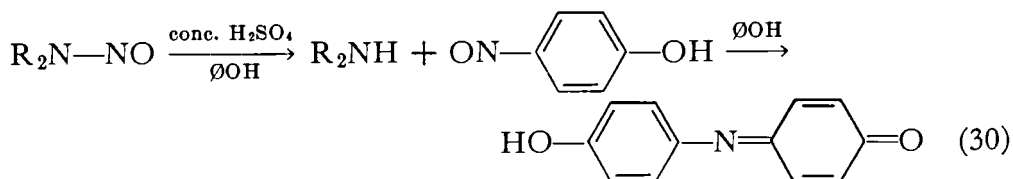
ACIDS Aqueous mineral acids hydrolyze nitrosamines only very slowly; the reaction is easily reversible and cannot be brought to completion unless something is done to remove the nitrous acid formed. An effective means is to pass a stream of hydrogen chloride through a solution of the nitrosamine in butyl ether or tetrahydrofuran for 30 minutes; other useful methods are refluxing with urea in alcoholic sulfuric acid^{79a} or, better, hydrogen chloride, or adding a mild reducing agent, such as a cuprous or ferrous salt, to convert the nitrous acid to nitric oxide.^{79b} (Eq. 28). These procedures have the additional advantage of preventing



the nitrous acid from attacking the amine at other sites, such as nitrosating the *para* position of an N-aryl group. Indeed, in the absence of nitrous acid scavengers, N-nitroso anilines undergo the Fischer-Hepp rearrangement,⁸⁰ a reaction now known to be intermolecular, forming *p*-nitroso anilines (Eq. 29). Another amine, such as dimethylaniline, can also be used to intercept the migrating nitrosonium ion.



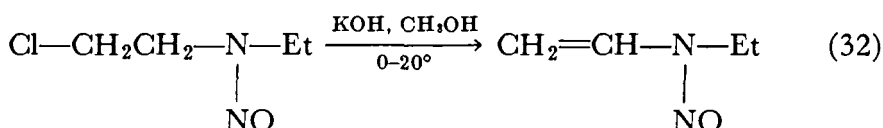
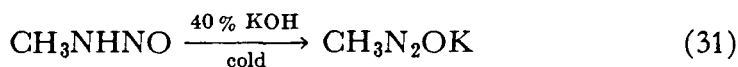
When nitrous acid (or derived species) is liberated from nitrosamines in the presence of phenol, it is scavenged by the phenol and converted through *p*-nitrosophenol to indophenol (Eq. 30). This is the basis of the



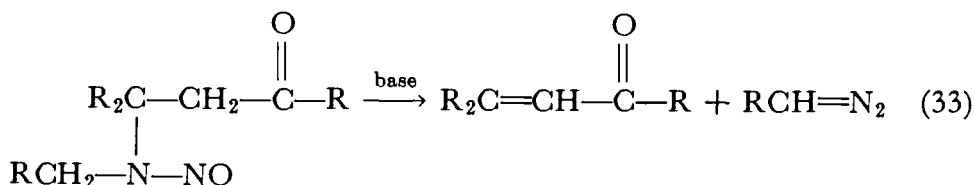
Liebermann nitroso test⁸¹; the indophenol is easily recognized by the fact that it is red in the acid solution in which it is formed, but changes to blue when diluted and made basic. Alkyl nitrites also give this test.

N-Nitroso amides can be reconverted to the parent amide by treatment with hydrogen chloride in an inert solvent, but acyl-nitrogen cleavage may compete, as in the case of N-nitroso lactams, which give ω -chloro acids or unsaturated acids.⁸² However, good conversions to amides have been obtained by treating N-nitroso amides with hydrogen bromide and sodium thiosulfate, by which the nitro group is removed as nitrosyl bromide and then destroyed by reduction, and by treatment with hydrogen chloride in the presence of phenol or sodium bisulfite.^{74a}

BASES Simple nitrosamines are not at all readily attacked by bases, apart from the conversion of primary nitrosamines to salts⁸³ (Eq. 31). β -Chloroethylnitrosamines can even be dehydrohalogenated to vinyl-nitrosamines by alcoholic alkali⁸⁴ (Eq. 32). In the special case of N-



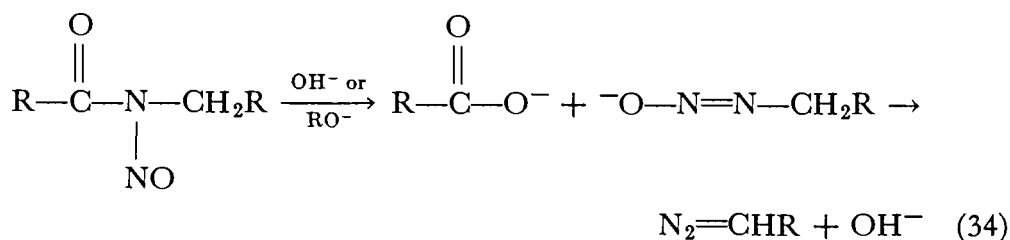
nitroso-N-methyl-*p*-nitroaniline, nucleophilic displacement of the N-aryl group has been observed,⁸⁵ giving rise to *p*-nitrophenol and diazomethane. A carbonyl group attached to a β -carbon activates the β -hydrogen and thus promotes elimination of one alkyl group, which appears as an α,β -unsaturated ketone (Eq. 33).⁸⁶ This reaction is most familiar in its



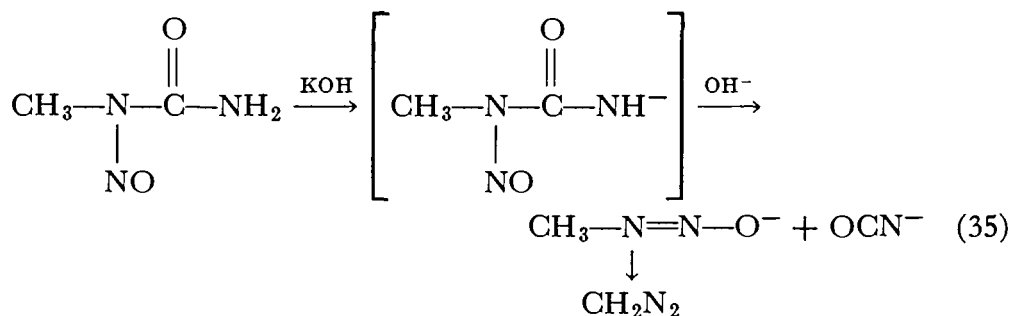
application to the preparation of diazomethane from the nitrosated adduct of methylamine and mesityl oxide.

N-Alkyl N-nitroso amides are more or less easily cleaved to diazoalkanes by base, as has been discussed in Chapter 10 (*q.v.*) in connection with preparative methods. Attack must in general be on the carbonyl group, which is thereby removed, leaving an alkyl diazotate. The latter are very

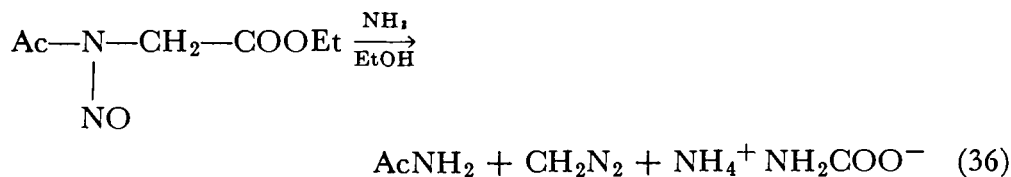
unstable and break up spontaneously at room temperature or on slight warming to give a diazoalkane ⁸³ (Eq. 34). N-Methyl-N-nitroso-urea,



which reacts with aqueous alkali without heating, gives rise to cyanate ion as well as diazomethane on alkaline degradation ^{76b, 87}; this product is best accounted for if it is supposed that the base functions by removing an amide proton (Eq. 35).

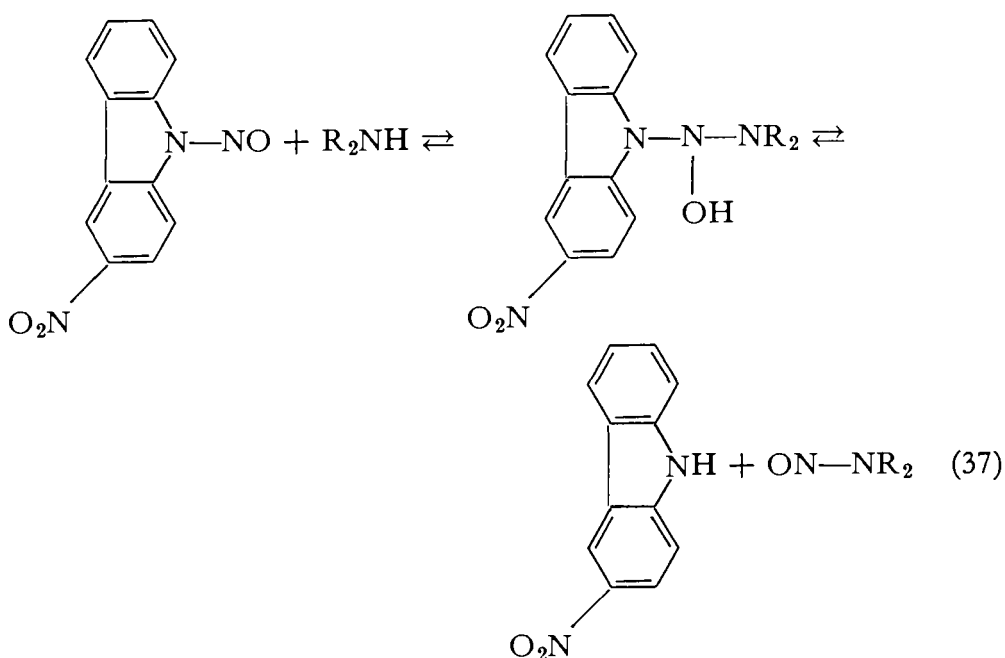


The N-nitroso-N-acyl derivatives of α -amino esters constitute a special case; alcoholic ammonia is sufficient to convert them to diazoalkane with concomitant loss of the carboalkoxy group as carbamate ⁸⁸ (Eq. 36). The reaction is evidently a cyclic process, for isotopic labeling experiments



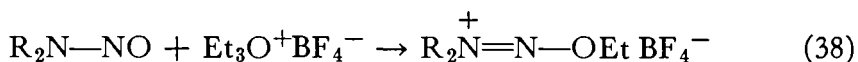
have shown that the nitroso oxygen ends up in the carbamate ion.

The ability of certain N-nitrosocarbazoles to act as nitrosating agents towards secondary amines may be mentioned in connection with the action of bases, for there are features of the reaction that suggest that it is not simply a case of solvolysis to give nitrous acid.³¹ It has been suggested that the nitroso transfer takes place through formation and breakdown of a hydroxytriazane (Eq. 37).



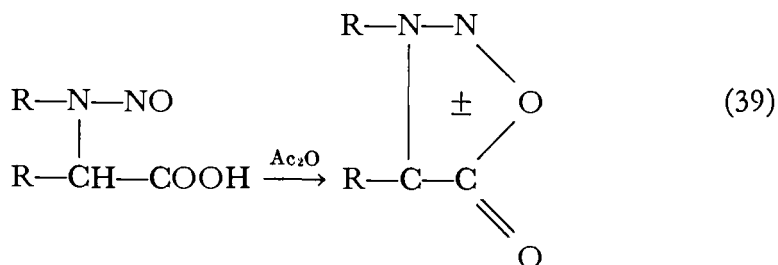
ALKYLATION Secondary nitrosamines have been alkylated by triethyloxonium fluoborate and by methyl or ethyl iodide in the presence of silver perchlorate⁸⁹ (Eq. 38). The products bear the added alkyl group on oxygen, for reduction gives only *unsym*-dialkyl hydrazine. They are stable in hydroxylic solvents, but are destroyed by base. (Com-

pounds of the isomeric structure, $\text{R}_3\text{N}^+\text{---NO} \text{BF}_4^-$, are apparently formed from tertiary amines and nitrosyl fluoborate—see Chapter 2). Primary nitrosamines have been alkylated in the form of their salts (metal dia-



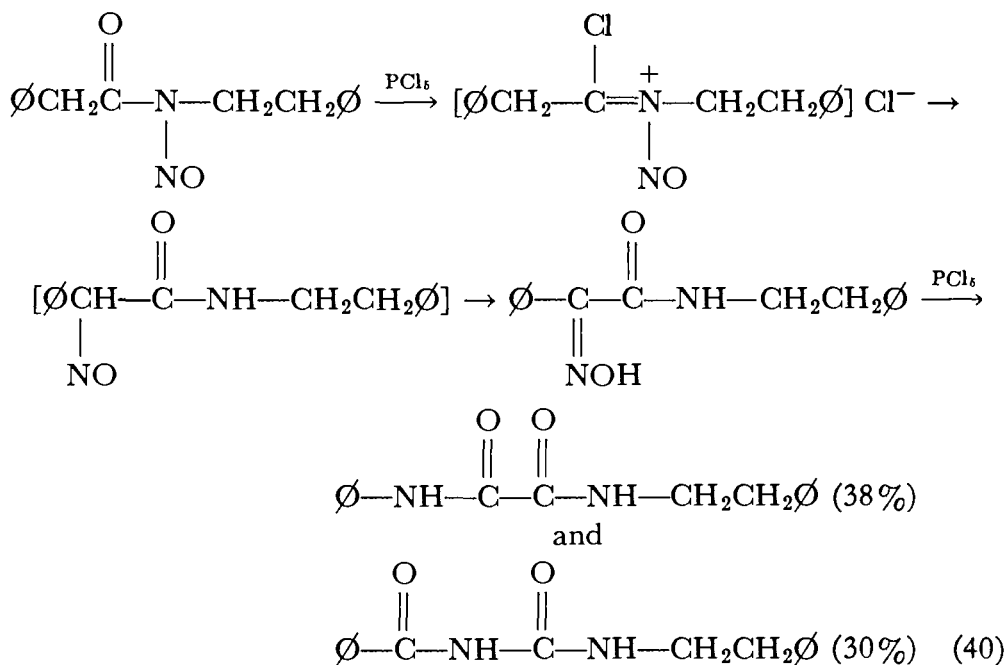
zotates); sodium salts yield secondary nitrosamines (N-alkylation), whereas silver salts give the isomeric diazo ethers (O-alkylation).^{8b, 90}

ACYLATION Simple nitrosamines do not appear to be affected by acylating agents, but α -carboxy nitrosamines (α -nitrosamino acids) undergo the important reaction of sydnone formation⁹¹ (Eq. 39). The

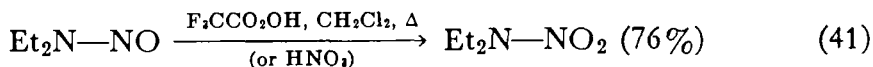


cyclization with acetic anhydride requires several hours at steam-bath temperatures or several days at room temperature, but trifluoroacetic anhydride accomplishes it in a few seconds; carbodiimides may also be used. α -Cyano nitrosamines are cyclized by hydrogen chloride alone; the products are sydnone imines.⁹²

N-Nitroso amides rearrange when treated with the inorganic acylating agent phosphorus pentachloride.⁹³ The reaction apparently involves several distinct steps, resulting in formation of an oxime and subsequent Beckmann rearrangement (Eq. 40). The mechanism by which the nitroso group is transferred from nitrogen to carbon is not clear.



OXIDATION Secondary nitrosamines are oxidized to nitramines in good yield by peroxytrifluoroacetic acid^{94a} and by nitric acid^{94b} (Eq. 41); although the reaction with the latter reagent is in effect an oxidation, it



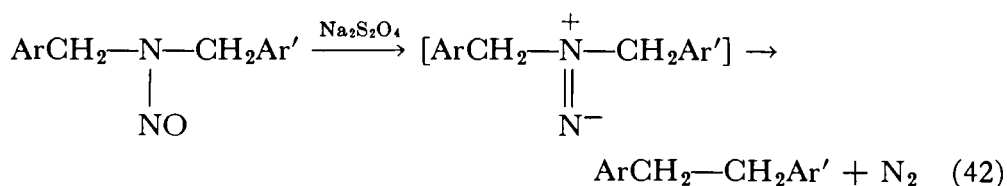
may perhaps proceed through nitrolysis. Only failures have been reported with other oxidizing agents.¹¹ Oxidation of primary nitrosamines (in the form of their salts, the diazotates, $\text{RN}=\text{NONa}$) by potassium ferricyanide occurs readily with both alkyl and aryl derivatives to give the corresponding nitramine^{14b} (cf. Chapter 11). The arenediazotates may also be oxidized by chlorine, which converts them to N-chloronitramines (which rearrange fairly quickly to chloroaryl nitramines).¹¹

The oxidation of N-nitrosoguanidine by potassium permanganate is

apparently the only reported instance of the successful oxidation of anything resembling an N-nitroso amide to an N-nitro amide.⁹⁶ However, a number of N-nitroso anilides have been converted nearly quantitatively to N-nitroso arylhydroxylamines by hydrogen peroxide,⁹⁶ a rather curious reaction whose path has not been elucidated.

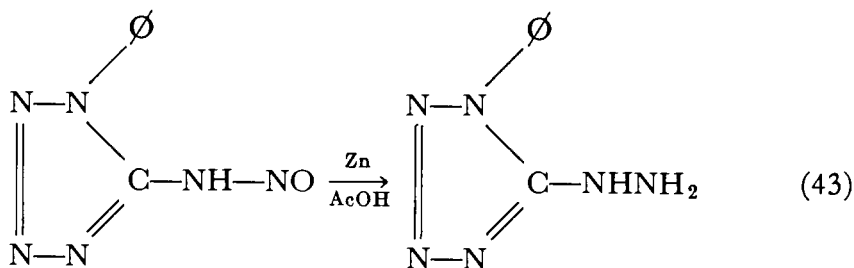
REDUCTION Reduction of nitrosamines in general takes three different courses: removal of oxygen to form an azamine or its decomposition products; replacement of oxygen by hydrogen to form a hydrazine; or cleavage of the N—N bond to form a secondary amine. These formally represent successive stages of reduction, but although such a succession may occur, there is reason to believe that the respective products are ordinarily reached by separate paths.

Simple oxygen removal has been accomplished with sodium dithionite or with lithium in liquid ammonia.⁹⁷ The products are those obtained from azamines produced in other ways, such as the oxidation of *unsym*-disubstituted hydrazines (see Chapter 9): tetrazenes or bialkyls (Eq. 42). The bialkyls are evidently formed by union of the alkyl radicals within the solvent cage, for there is no crossover to form symmetrical



bialkyls when an unsymmetrical nitrosamine is used.^{97b} Triphenylphosphine, which removes oxygen from C-nitroso groups, reportedly will not deoxygenate nitrosamines.⁹⁸

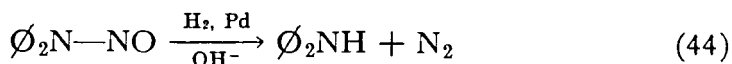
Reduction of both primary and secondary nitrosamines to hydrazines can generally be accomplished smoothly with zinc dust and acetic acid^{7, 99} (Eq. 43); lithium aluminum hydride, used in tetrahydrofuran, is also



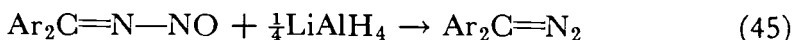
generally successful.¹⁰⁰ Primary nitrosamines in the form of their sodium salts have also been reduced to hydrazines with aluminum turnings and aqueous alkali.^{14b} Catalytic hydrogenation of secondary nitrosamines over a platinum, palladium, or rhodium catalyst also gives rise to hydrazines; cleavage to secondary amine is a more or less important competing reac-

tion, but addition of certain salts, such as calcium chloride, magnesium sulfate, or ammonium acetate, represses its inroads.¹⁰¹

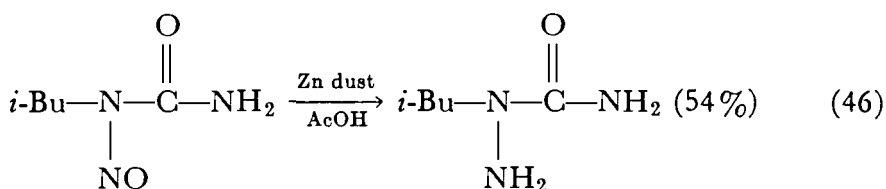
Reduction to secondary amines is accomplished by sodium amalgam in alcoholic hydrochloric^{102a} or acetic acid, by hydrogenation over Raney nickel,¹⁰¹ and by vigorous hydrogenation over other catalysts, such as palladium, especially in the presence of base^{102b} (Eq. 44).



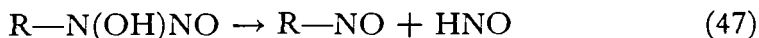
Nitrosimines are reduced by a limited quantity of lithium aluminum hydride to diazoalkanes¹⁰ (Eq. 45).



Careful reduction of N-nitroso amides, most generally by zinc dust and acetic acid, leads to hydrazides, but, of course, reduction must compete with both hydrolysis of the nitroso group and the rather easy rearrangement of nitroso amides. Consequently, yields are often low, and with tertiary N-alkyl groups, negligible. Reduction of nitroso amides has seen its greatest application with nitrosourethans¹⁰³ and nitrosoureas¹⁰³⁻¹⁰⁵ (Eq. 46).



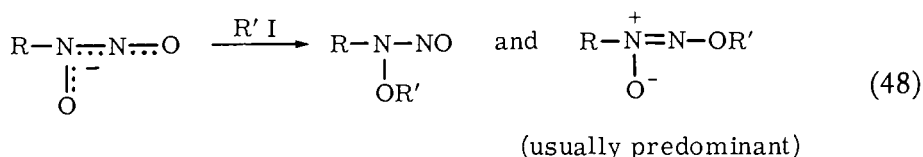
NITROSOHYDROXYLAMINES¹¹ Although their ability to form metal chelates overwhelmingly dominates the chemistry of N-nitrosohydroxylamines, there are other interesting features. They are generally unstable to storage (except as their salts); it seems likely that the first step is loss of nitroxyl to leave a nitroso compound (Eq. 47). When N-nitroso-N-



benzylhydroxylamine is decomposed (most cleanly in glacial acetic acid), dimeric α -nitrosotoluene is, indeed, the major product.^{106a} The same result is observed when N-nitroso-N-phenylhydroxylamine is warmed with mineral acid.^{106b} With N-nitroso-N-alkylhydroxylamines, the preferred path for acid-catalyzed decomposition appears to be loss of nitrous oxide and formation of an alcohol and/or olefin (cf. the discussion of nitramines, ahead), but studies of the subject are very limited.¹⁰⁷ O,N-Dialkyl-N-nitrosohydroxylamines, however, give nitrogen, an alcohol, and an aldehyde.¹²

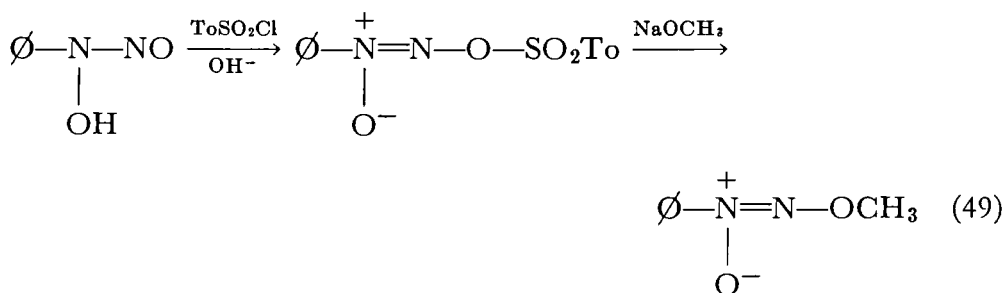
Alkylation of salts of N-nitrosohydroxylamines produces one or both

of two isomeric products, resulting from substitutions at one oxygen or the other ^{13, 108} (Eq. 48); both products are distinct from the isomeric O,N-disubstituted nitramines (see ahead). The structure of one isomer is established by independent synthesis from alkoxyamines and nitrous acid; the structure of the other isomer was controversial for many years and

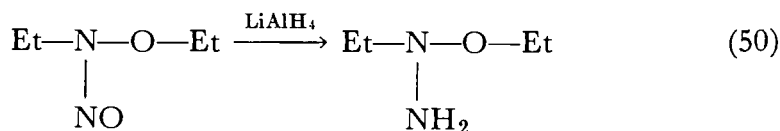


was once thought to be that of a diimide dioxide ¹⁰⁸ (now known to be the structure of dimeric C-nitroso compounds). Chemical evidence was in some respects ambiguous, but the demonstration that the dibenzyl compound obtained from benzylation of N-nitroso-N-benzylhydroxylamine has two distinct proton signals in its NMR spectrum has resolved ¹³ the question in favor of the azoxy structure shown in Equation 48.

Acylation with toluenesulfonyl chloride takes place on the nitroso oxygen to give a product of azoxy structure; treatment with sodium methoxide converts this to the corresponding product of direct methylation ^{108a} (Eq. 49). Reduction ordinarily cleaves the N—N bond, giving



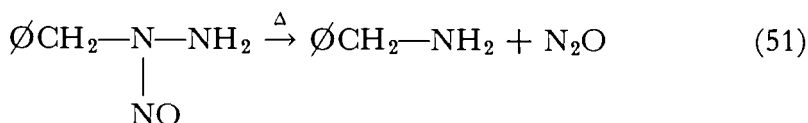
either the parent hydroxylamine or the corresponding amine,¹² but in one case, N-nitroso-O,N-diethylhydroxylamine, lithium aluminum hydride produced a hydroxyhydrazine derivative ¹⁰⁹ (Eq. 50). Oxidation of N-nitroso-N-phenylhydroxylamine with either permanganate or hypo-



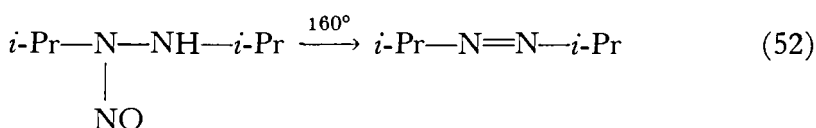
chlorite gives nitrosobenzene.¹¹⁰

NITROSOHYDRAZINES Although nitrosohydrazines are known in considerable variety, few of them are stable to storage. N-Substituted

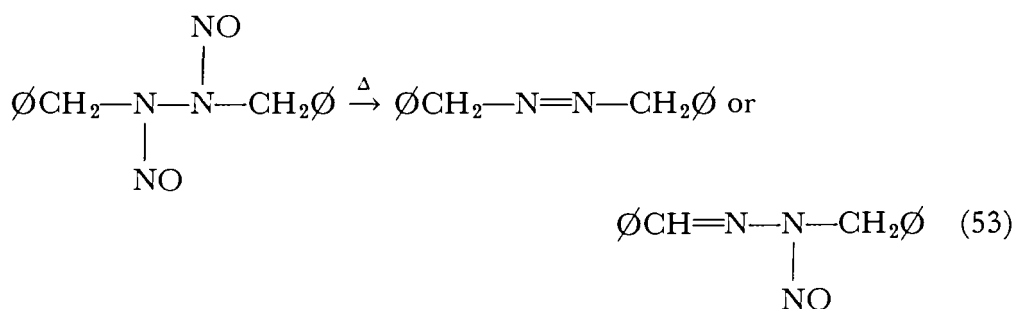
N-nitroso hydrazines lose nitrous oxide on heating and are thereby converted to amines ^{14b, 111} (Eq. 51). N-Nitroso-*sym*-dialkyl hydrazines appear to be more resistant to heat, for N-nitroso-N,N'-diisopropylhydra-



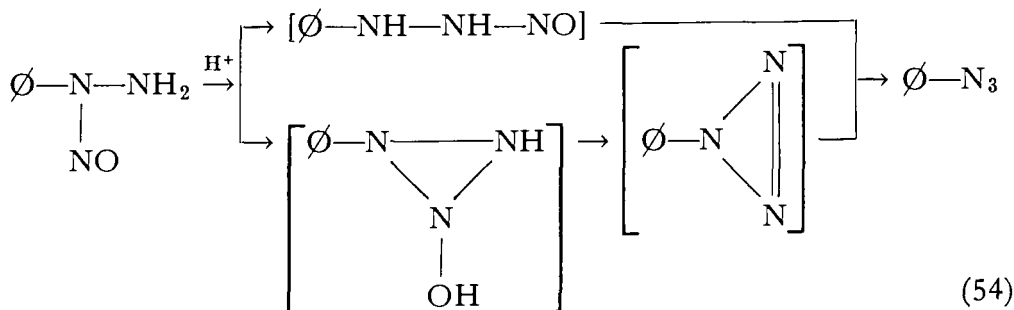
zine decomposes only when heated to 160°, and then gives 2,2'-azopropane ¹¹² (Eq. 52). The *sym*-dinitrosohydrazines decompose much more easily, even slowly at room temperature, to give either azo compounds



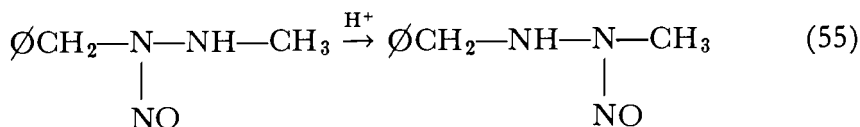
or nitroso hydrazones ^{14b, 113} (Eq. 53).



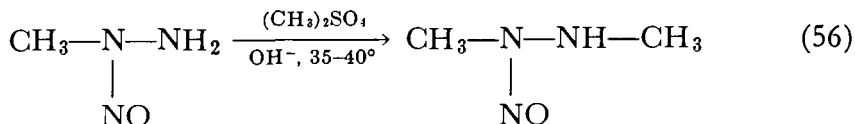
Acids cause the dehydration of monosubstituted nitrosohydrazines to azides with variable success. It has been shown ¹¹¹ by experiments with ¹⁵N-labeled compounds that phenyl azide is formed from N-phenyl-N-nitrosohydrazine largely through nitroso migration to the presumed intermediate N'-nitroso compound, but also to some extent by an isotope-scrambling path that perhaps involves a cyclic intermediate (Eq. 54). *Sym*-dialkyl nitrosohydrazines are slowly but generally cleanly hydrolyzed



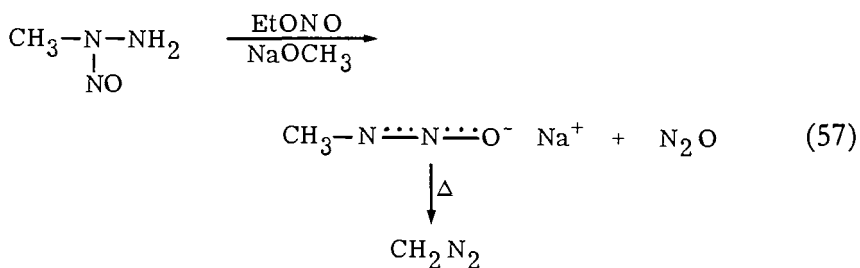
to the parent hydrazine by strong mineral acid,^{14b, 112} but wandering of the nitroso group may first occur if the two alkyl groups are different (Eq. 55).



Monosubstituted nitrosohydrazines undergo alkylation (Eq. 56) or acylation (Schotten-Baumann conditions) normally at the unsubstituted

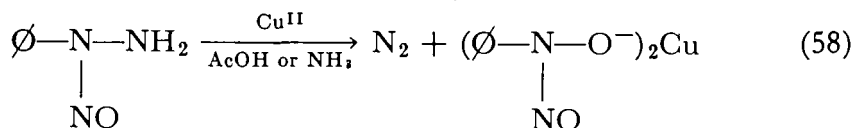


nitrogen.^{14b} Treatment with ethyl nitrite in the presence of sodium alkoxides, however, results in a more profound change, producing alkanediazotates (i.e., salts of primary nitrosamines) in their more stable “iso” modification^{14b} (Eq. 57); this reaction, which appears to be general;



probably involves formation of methylnitrosamine in the same way that the amino group of ordinary *unsym*-disubstituted hydrazines is removed by means of nitrosation (see Chapter 9). Aldehydes and ketones readily react at the unsubstituted amino group to form nitroso hydrazones.^{14b, 114}

Reduction of N-nitroso hydrazines has been accomplished with lithium aluminum hydride, sodium amalgam, or catalytic hydrogenation; at least one N—N bond is inevitably broken, and no triazane has yet been obtained.^{14a} Oxidation has been very little investigated, and the only report concerns the reaction between cupric compounds and N-phenyl-N-nitrosohydrazine. Essentially, neutral cupric acetate simply forms an isolable but unstable copper salt, but in acetic acid or ammoniacal solution, the amino group is replaced by hydroxyl, giving the copper chelate of N-nitroso-N-phenylhydroxylamine¹⁰⁶ (Eq. 58).

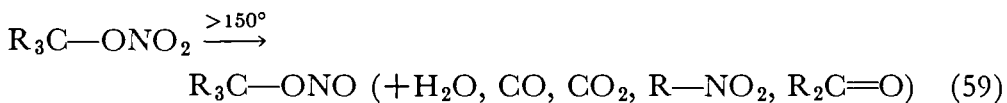


A considerable number of N-nitroso hydrazones and N-nitroso hydrazides are known; for the most part, little beyond their preparation

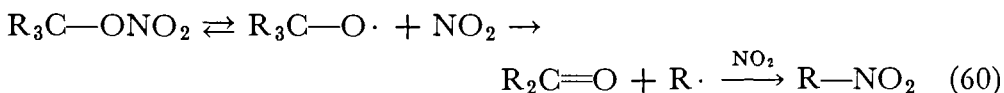
and identifying properties has been reported. The literature concerning them can be found among the references cited in the foregoing paragraphs and other papers by the authors cited.

D. Nitrates ⁴¹

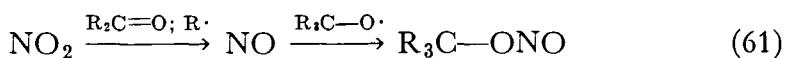
HEAT AND LIGHT Alkyl nitrates in general decompose at temperatures above about 150°; the decomposition may be controlled up to about 200–250°; but the high activation energy (~40 kcal) leads easily to explosive reaction. When the exposure to heat is not prolonged, the corresponding alkyl nitrite is formed, in yields as high as 75% along with some nitroalkane of fewer carbons (Eq. 59); the lost oxygen atom is found bound up in water and the oxides of carbon. When the alkyl group is tertiary, a ketone may be found among the products.⁴¹ The



evidence of kinetics ^{115–117} and the nature of the products points clearly to an initial dissociation into an alkoxyl radical and nitrogen dioxide; the familiar cleavage of alkoxyl radicals into a carbonyl compound and an alkyl radical, which can combine with nitrogen dioxide, accounts for the nitroalkane observed (Eq. 60). Reduction of nitrogen dioxide by the carbonyl compound or the alkyl radicals produces nitric oxide, which



combines with more alkoxyl radical to give the observed nitrite (Eq. 61).



Accordingly, the formation of nitroalkane becomes more important in proportion to the stability of the alkyl radical that can be cleaved from the alkoxyl radical.¹¹⁶

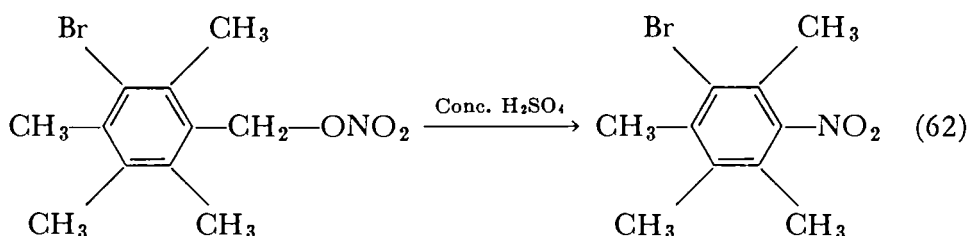
Nitric oxide accelerates thermal decomposition of nitrates, but nitrogen dioxide retards it; these facts are readily accounted for if it is assumed that the initial dissociation step is reversible ¹¹⁵ (Eq. 60). An excess of nitric oxide converts nitrates efficiently to nitrites by scavenging the alkoxyl radicals; this reaction is not a bimolecular displacement on oxygen, for it does not follow second-order kinetics.⁷²

Photolysis of nitrates has attracted much less attention than that of nitrites, a circumstance probably due to the fact that the products are not so interesting. Photolysis of ethyl nitrate at 95°, for example, produces a rather unrewarding mixture of formaldehyde, acetaldehyde, nitromethane, hydrogen, and oxides of carbon and nitrogen.¹¹⁸ It appears

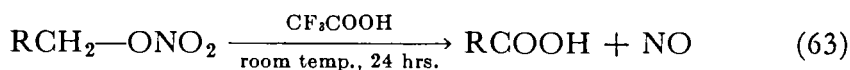
probable that here, too, the initial step is cleavage to form an alkoxy radical.

ACIDS Even strong mineral acids have little or no accelerating effect on hydrolysis or alcoholysis of alkyl nitrates.^{119, 120} Protonation evidently occurs in concentrated sulfuric acid, however, for the freezing-point lowering corresponds to a Van't Hoff *i*-factor of 5, which can be accounted for by solvolysis into an alkyl hydrogen sulfate and nitronium ion; as a consequence, alkyl nitrates in concentrated sulfuric acid are potent nitrating agents¹²¹ (see ahead).

Certain fully substituted benzyl nitrates undergo degradation involving loss of the benzylic methylene group when treated with concentrated sulfuric acid¹²²; presumably this takes place through electrophilic displacement by the released nitronium ion (Eq. 62). Some other primary



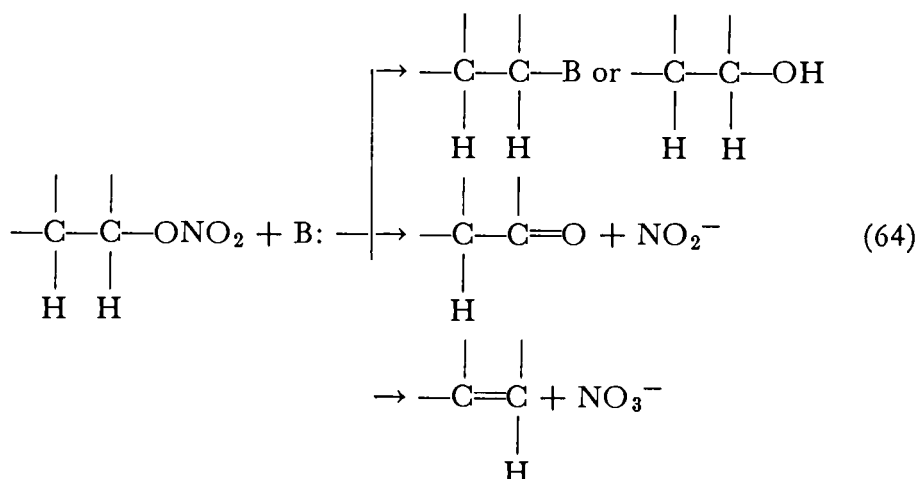
alkyl nitrates have been found¹²³ to undergo oxidative cleavage when treated with trifluoroacetic acid, but not with sulfuric acid, curiously enough (Eq. 63). This reaction is accelerated by ultraviolet radiation,



although it also proceeds in the dark. Other workers have reported degradation of ethyl nitrate to formic acid¹²⁴ and of 2-octyl nitrate to 2-octanone¹²⁵ by treatment with 70 to 90% sulfuric acid. Nevertheless, the general inertness of alkyl nitrates to strong acid is shown by the many examples of successful preparation of alkyl nitrates by treatment of alcohols with a mixture of nitric and sulfuric acids.

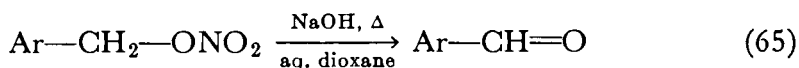
Contact with strong Lewis acids, such as boron fluoride or stannic chloride, causes rapid decomposition or even explosion of alkyl nitrates^{124, 126}; esters, acids, and aldehydes are produced, usually in low yields.

BASES Bases act on alkyl nitrates in three distinct ways: attack at C or N, resulting in saponification; attack at an α -hydrogen, resulting in elimination of nitrous acid and formation of a carbonyl compound; and attack at a β -hydrogen, resulting in elimination of nitric acid and formation of an olefin (Eq. 64). The first and last of these processes may also



take place by first-order solvolysis through a carbonium ion. In the absence of activating structural features, however, all of these reactions are slow, usually requiring boiling with aqueous or alcoholic alkali, and simple alkyl nitrates can be regarded as only sluggishly reactive. As might be anticipated on the basis of the weakness of nitric acid compared to hydrobromic, displacement reactions of alkyl nitrates are much slower (*ca.* $\frac{1}{40}$) than those of the corresponding bromides. As a general consequence, the O-nitro group has value as a protecting group in synthesis, and will in favorable cases even stand up to the conditions used for the saponification of a carboxylic ester elsewhere in the molecule.¹²⁷

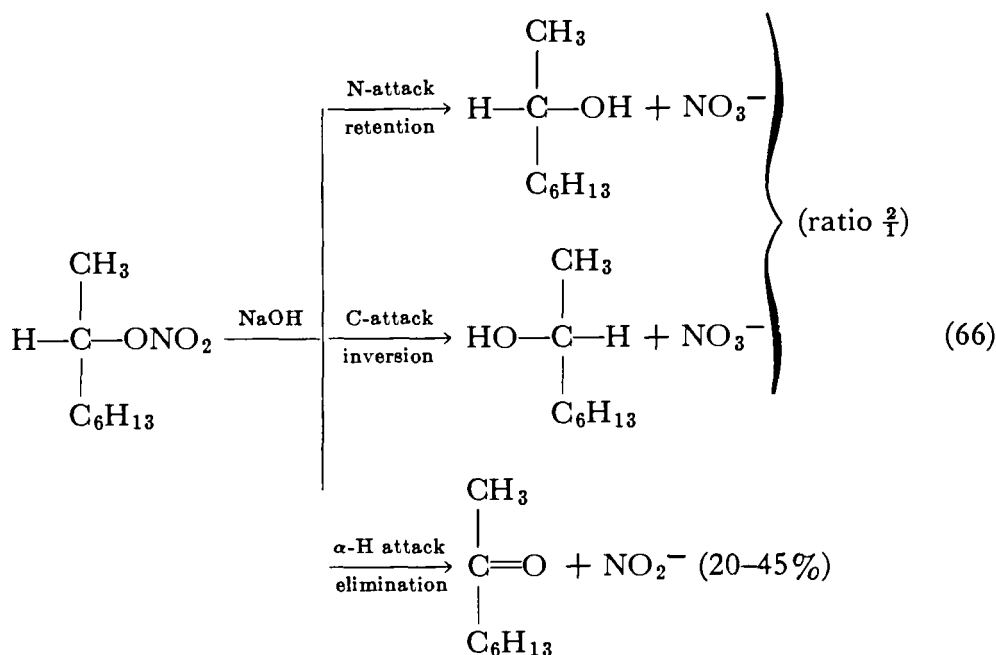
Primary alkyl nitrates ordinarily undergo hydrolysis in preference to the elimination reactions, and methyl nitrate appears to react with base solely by displacement.¹²⁸ Benzyl nitrates, however, undergo the elimination reaction more readily to give benzaldehydes¹²⁸ (Eq. 65), and when electron-withdrawing substituents are present, aldehyde formation^{129, 130} may exceed 90%. The ease of this reaction may be correlated with the



electron density about the α -hydrogen as revealed by NMR; the O-nitro group itself brings about a marked downfield shift with respect to the corresponding alcohol or carboxylic ester.¹³⁰

With secondary alkyl nitrates, elimination to form a carbonyl compound is of increased importance, but is still the minor reaction, accounting for 8 to 45% of the product in the absence of activating substituents.^{125, 127} The reaction of 2-octyl nitrate with alkali has been studied both kinetically and polarimetrically¹²⁵; the overall reaction is second order, and the 2-octanol produced shows about 70% retention of the optical configuration at the α -carbon. Assuming that there is no racemization before saponification, the results indicate that hydroxide ion

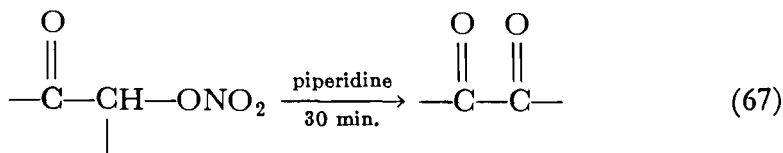
attacks the nitrogen in preference to carbon in a ratio of about 2:1 (Eq. 66). Although some of the inverted alcohol can be expected to have



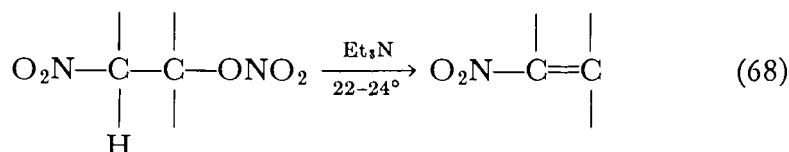
arisen through first-order dissociation into a carbonium ion, the amount must be small, in view of the second-order kinetics. Neutral solvolysis, by contrast, results in 85% inversion and may proceed principally by the unimolecular path.

With primary alkyl nitrates, bimolecular displacement on carbon would be expected to be of much greater relative importance, whereas with tertiary alkyl nitrates, saponification would be expected to proceed through attack on nitrogen or through unimolecular dissociation to the complete exclusion of bimolecular attack on carbon. In compounds where a β -hydrogen is present, such as *tert*-butyl nitrate, unimolecular solvolysis (which, of course, does not require base) leads to large amounts of olefin.^{128, 131}

If the potential acidity of the α -hydrogen is sufficiently increased, as it is by an adjacent carbonyl group, even such weak bases as aliphatic amines bring about formation of a carbonyl compound; in this way high yields of α -diketones have been obtained^{132, 133} (Eq. 67). When an acid-strengthening group is on a β -carbon, elimination with formation of an

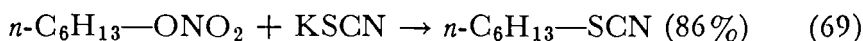


olefin is promoted and may become the predominant reaction ⁶¹ (Eq. 68).



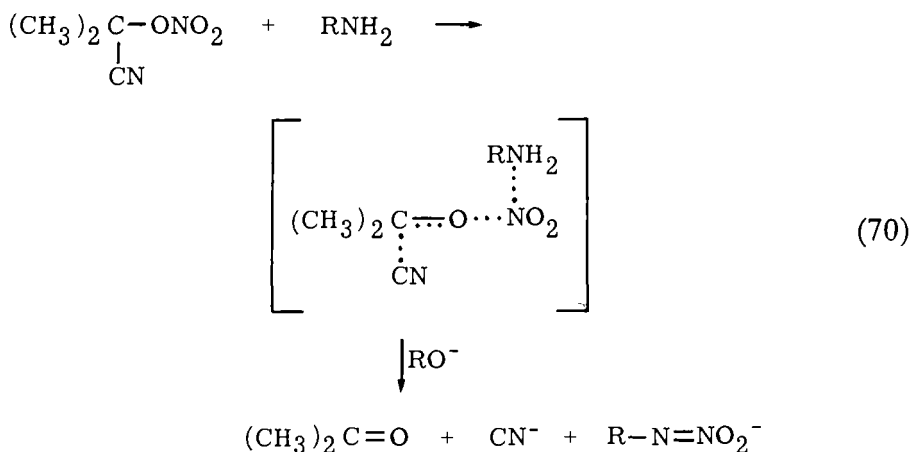
Energetic alkaline hydrolysis of polynitrates, such as nitroglycerine or nitrocellulose, brings about complete disruption of the molecule, with formation of nitrite, nitrate, cyanide, and ammonia.¹³⁴

OTHER NUCLEOPHILES Displacement of nitrate ion from carbon by other nucleophilic anions, such as iodide, cyanide, or thiocyanate, is a general, albeit somewhat slow, reaction of primary alkyl nitrates ¹³⁵ (Eq. 69). Sodium iodide in acetone has been used to replace a 6-nitroxy

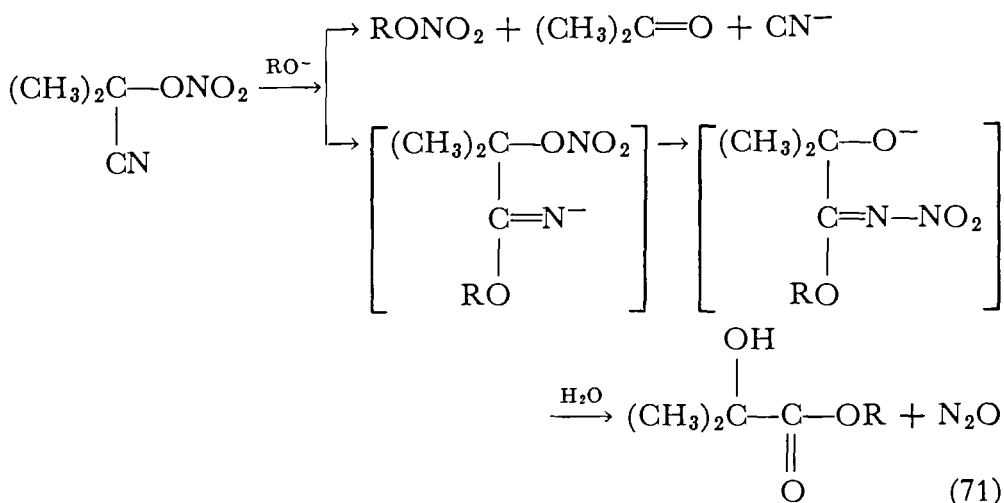


group in sugar derivatives by iodide,¹³⁶ and lithium chloride in acetone converts optically active α -phenylethyl nitrate to chloride with inversion.¹³⁷ Tertiary amines can be converted to quaternary ammonium nitrates in good yield,¹³⁸ and even primary and secondary amines ⁴¹ and hydrazine are alkylated ¹³⁹; aniline, on the other hand, attacks ethyl nitrate at the nitrogen to a significant extent and is thereby converted to phenylnitramine.¹⁴⁰

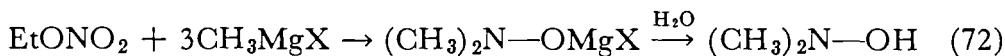
Attack by nucleophiles is shifted from carbon to nitrogen when the alkyl group is tertiary, so that *tert*-alkyl nitrates are useful as alkaline nitrating agents. α -Cyanoisopropyl nitrate (acetone cyanohydrin nitrate) is particularly reactive in this respect, because the anion that must be separated from nitrogen, R—O^- , can stabilize itself by fragmentation into cyanide and acetone ¹⁴¹ (Eq. 70). Strong bases, particularly alkoxides, may competitively attack the cyano group as well; the products



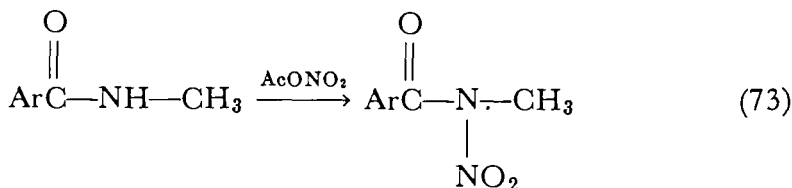
are then the α -hydroxyisobutyrate ester and nitrous oxide, formed presumably by intramolecular transfer of the nitro group from O to N (Eq. 71).



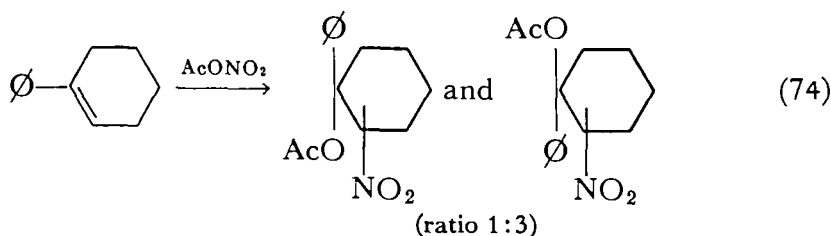
Carbanions derived from active methylene compounds, such as acetoacetic ester, attack primary alkyl nitrates principally at the α -carbon, and are thereby alkylated¹⁴²; if C-nitration is desired, α -cyanoisopropyl nitrate should be used^{41, 141} (cf. Chapter 14, "Preparative Methods"). Grignard reagents, however, attack even primary alkyl nitrates at nitrogen and produce N,N-dialkylhydroxylamines (Eq. 72) through a series of steps probably involving reduction to a nitrosoalkane.¹⁴³



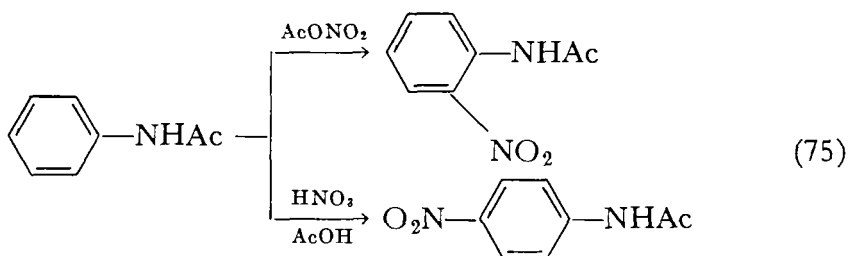
AS ACIDIC NITRATING AGENTS Both alkyl and acyl nitrates have significance as nitrating agents under acidic conditions. N-Nitration of amides, such as N-ethylurethan, has been accomplished with ethyl nitrate and sulfuric acid¹⁴⁴ and by acetyl nitrate¹⁴⁵ (Eq. 73). Acetyl nitrate adds



to olefins to form β -acetoxy nitroalkanes¹⁴⁶ (Eq. 74). Both alkyl and

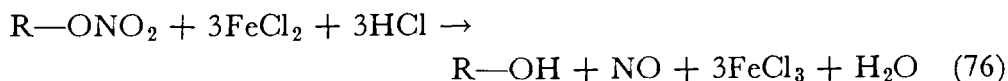


acyl nitrates act as nitrating agents toward aromatic hydrocarbons,⁴¹ and the latter will function even without the addition of sulfuric acid. This feature is particularly useful when dealing with acid-sensitive compounds, as is demonstrated by the successful nitration of diazocyclopentadiene with benzoyl nitrate.¹⁴⁷ The action of alkyl and acyl nitrates as nitrating agents is not in all circumstances simply to serve as a source of nitronium ion (although it must often be so), for the isomer ratios in the products are sometimes quite different from those obtained with nitric acid. The nitration of toluene, for example, which ordinarily gives more of the *ortho* isomer than the *para*, gives progressively higher proportions of *p*-nitrotoluene with alkyl nitrates (in polyphosphoric acid) as the bulk of the alkyl group is increased.¹⁴⁸ Although acetyl nitrate gives the same ratio of *ortho*- to *para*-nitrotoluene as does a mixture of sulfuric and nitric acids (cf. Chapter 14), its action on acetanilide quite markedly favors *ortho* substitution¹⁴⁹ (Eq. 75).



REDUCTION Alkyl nitrates are reduced by a wide variety of reagents to the corresponding alcohol and nitrogen, nitric oxide, nitrous oxide, or ammonia. Since the conditions required are mild and the yields are high, reduction has a distinct advantage over saponification as a means to regenerate alcohols from their nitrates. Indeed, the ease of reductive cleavage combined with the general inertness of nitrate esters to oxidizing agents (e.g., chromic acid) as well as bases recommends the nitro group for use as a protective group during other synthetic operations.¹²⁷

Zinc and acetic acid at room temperature have been used to cleave nitrates successfully in both the carbohydrate¹³⁶ and steroid fields.¹²⁷ Ferrous chloride reduces nitrates quantitatively to nitric oxide, thereby providing a useful analytical method¹⁰ (Eq. 76). Lithium aluminum



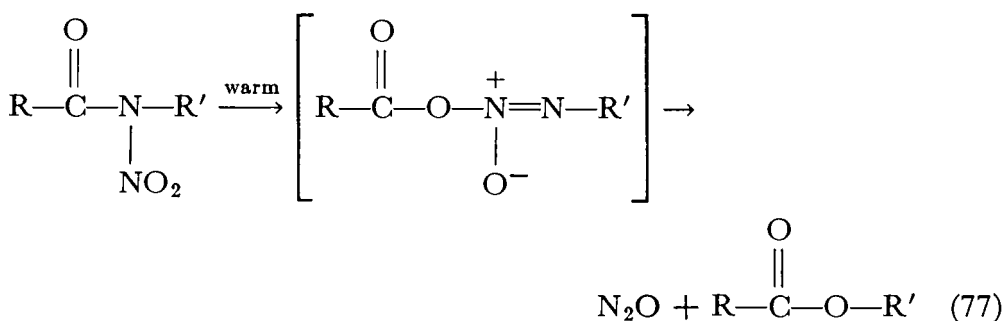
hydride^{68, 137} also reduces nitrates, generally quantitatively. Electrolytic reduction,¹⁵¹ sulfides,¹⁵² and catalytic hydrogenation^{125, 153} also give good yields of alcohol. Hydrazine when quite concentrated converts alkyl nitrates to alcohols, but when it is used in dilute solution, its principal

action is to attack the α -carbon and form alkyhydrazines.^{153, 154} It is not clear whether the conversion to alcohol proceeds through nucleophilic attack on the nitro group or in some other manner; the kinetics are of higher order than second,¹⁵⁴ and the C—O bond is evidently undisturbed, for optically active 2-octyl nitrate is converted to 2-octanol with retained configuration.¹⁵⁵ The inorganic products—nitrite, nitric oxide, nitrogen, ammonia, and azide—could reasonably be derived from decomposition of nitrohydrazine formed initially. In the presence of a hydrogenation catalyst (Pt or Pd), on the other hand, alcohol is the sole organic product,^{156, 157} and the reaction is most likely a true reduction. Cleavage of nitrates by hydrazine lends itself to stepwise denitration of polynitrates, such as PETN.¹⁵⁸

E. Nitramines^{11, 20}

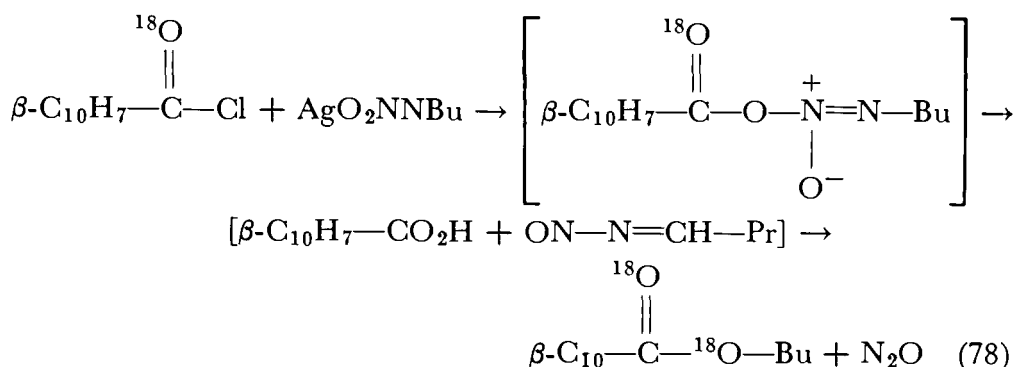
HEAT Nitramines in general appear to be less sensitive to heat than nitrate esters and in this respect parallel the relationship between nitrosamines and nitrite esters. Primary nitramines are less volatile than secondary nitramines, however, and attempts to distill them have led to decomposition. Methylnitramine gives rise to methanol, nitrous oxide, N,N-dimethylnitramine, and O,N-dimethylnitramine¹⁵⁹; the formation of the last two substances suggests the presence of an intermediate with pronounced methylating ability.

N-Nitro amides, like N-nitroso amides, decompose at much lower temperatures than their nonacylated counterparts; refluxing in hexane is sufficient to cause loss of nitrous oxide and formation of an ester^{74a} (Eq. 77). It is probable that the first step is rearrangement to an O-acyl N-alkyl



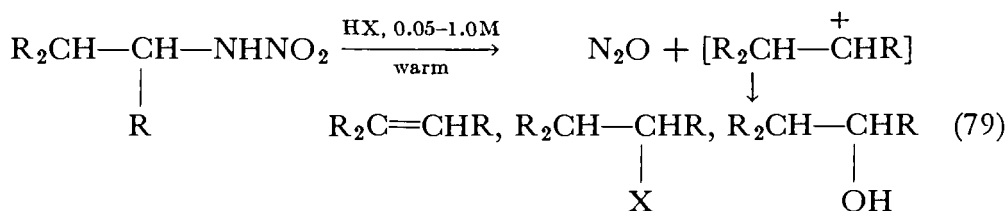
nitramine, for when the preparation of such compounds is attempted by the reaction of the silver salt of a primary nitramine with an acid chloride, the same decomposition products are obtained.⁷⁵ When the N-alkyl group is primary (i.e., *n*-butyl), the decomposition apparently parallels that of N-nitroso amides, for when the reaction is begun with excess ¹⁸O in the carbonyl group, the ¹⁸O isotope distribution in the resulting ester is symmetrical; dissociation into an N-nitroso aldimine and a carboxylic

acid has been proposed to account for this result ⁷⁵ (Eq. 78). The

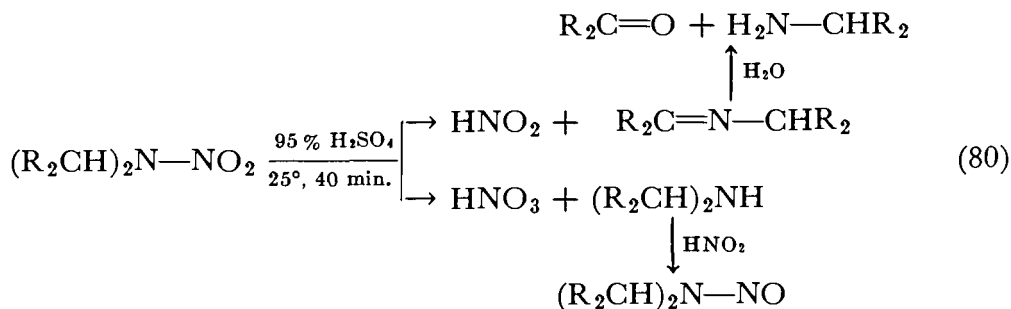


analogous reaction with a secondary N-alkyl group (cyclohexyl) is apparently entirely intramolecular, analogous to the behavior of N-*sec*-alkyl N-nitroso amides, for the isotopic individuality of the carbonyl oxygen is then largely retained in the ester produced.

ACIDS Primary nitramines are easily decomposed by warming with dilute mineral acid. The reaction is not simple hydrolysis, for the products are nitrous oxide and compounds that can be anticipated from formation of a carbonium ion as an intermediate ¹⁶⁰ (Eq. 79). Secondary

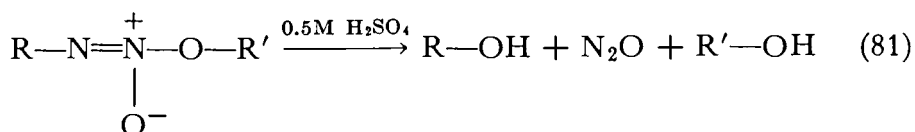


nitramines are much more resistant to acids, requiring nearly concentrated sulfuric acid for decomposition, and give quite different products,¹⁶¹ which can be accounted for if it is assumed that the principal reaction is elimination of nitrous acid to form a Schiff's base, accompanied by a small amount of simple hydrolysis (Eq. 80).

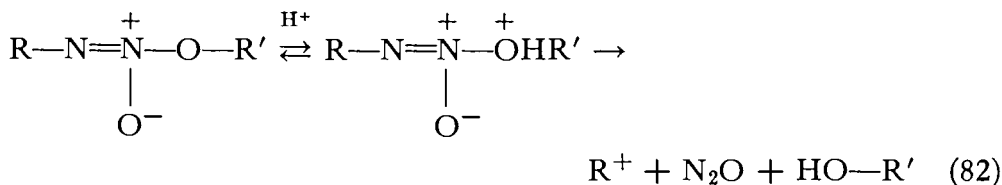


The acid-induced decomposition of primary nitramines has been much more thoroughly studied than that of secondary nitramines. The reac-

tion is second order kinetically and apparently subject to general acid catalysis¹⁶⁰; the alcohol obtained from (+)-*sec*-butylnitramine is completely racemized.¹⁶² A parallel reaction occurs with O,N-dialkyl nitramines (Eq. 81), which suggests that tautomerization of primary nitramines

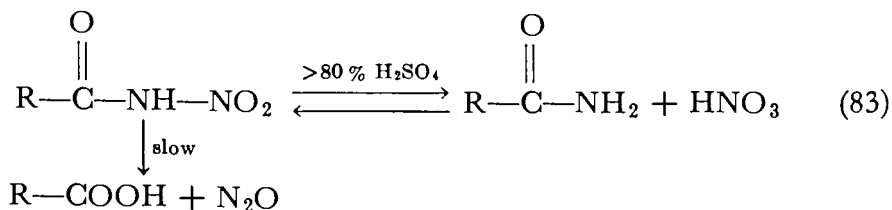


to the *aci*-nitro structure is an essential step. It has been established that the O-alkyl group never appears as a carbonium ion, for not only are none of the characteristic by-products of carbonium ion formation observed, but optical asymmetry at the site of attachment to oxygen is retained.¹⁶³ Electron-donating ability in the N-alkyl group accelerates the cleavage, but changes in structure of the O-alkyl group have little influence. In consideration of these facts, it has been proposed that the reaction proceeds by fragmentation (not necessarily concerted) of the conjugate acid formed by acquisition of a proton at the dicoordinate oxygen (Eq. 82). However, it would also be admissible for the reaction

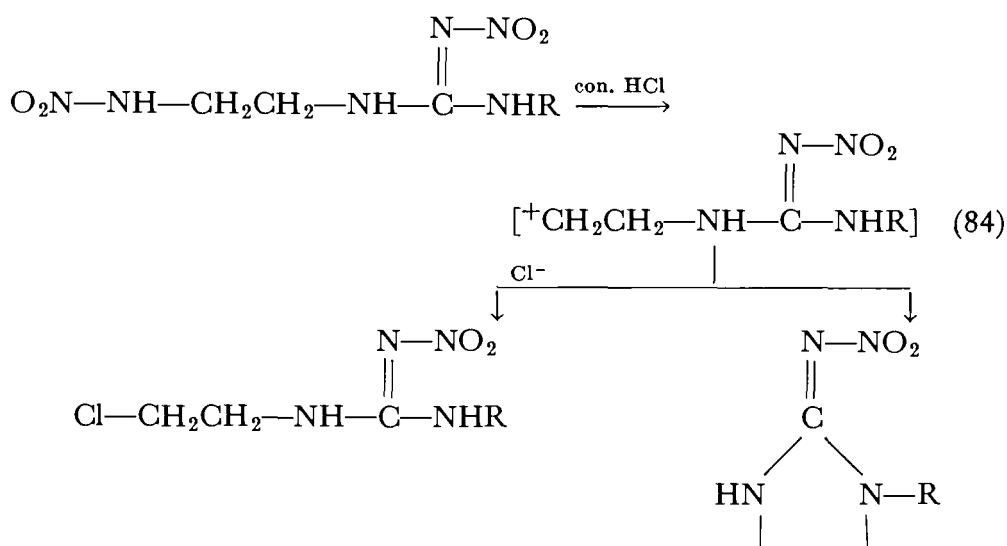


to proceed as does its isosteric analog, the Nef reaction (see Chapter 14), by attack of a water molecule at the original amine nitrogen to yield a nitroso hydroxylamine (analogous to the α -nitroso alcohol intermediate in the Nef reaction); N-nitroso hydroxylamines are, indeed, decomposed by sulfuric acid to form the same products as do nitramines.¹⁰⁷

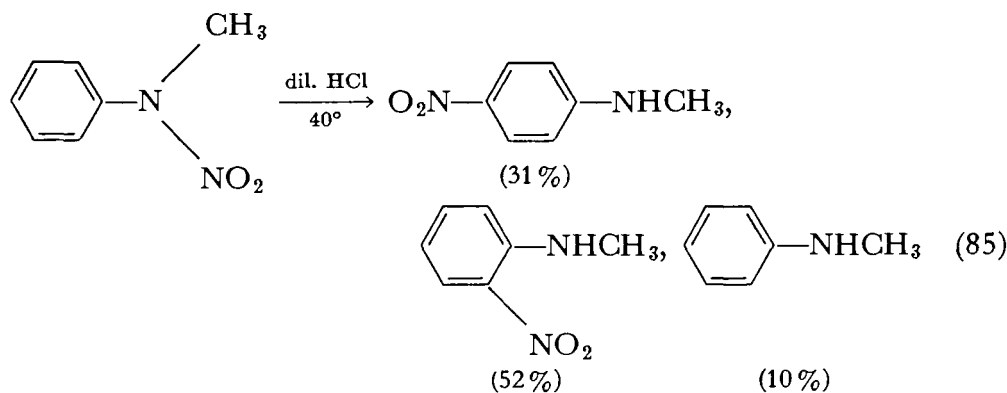
N-Nitro amides are also decomposed by strong acid, but not as readily as are alkyl nitramines. Solvolytic denitration predominates over decomposition to nitrous oxide, and indeed, in very strong acid, a nitration-denitration equilibrium may be set up^{161, 163} (Eq. 83). An instructive example of the difference in stability of different types of N-nitro structures



toward strong acid, and of the consequences of the formation of carbonium ions in the decomposition of primary nitramines, is encountered in the decomposition of N-(β -nitraminoethyl)-N'-nitroguanidines ¹⁶⁴ (Eq. 84).

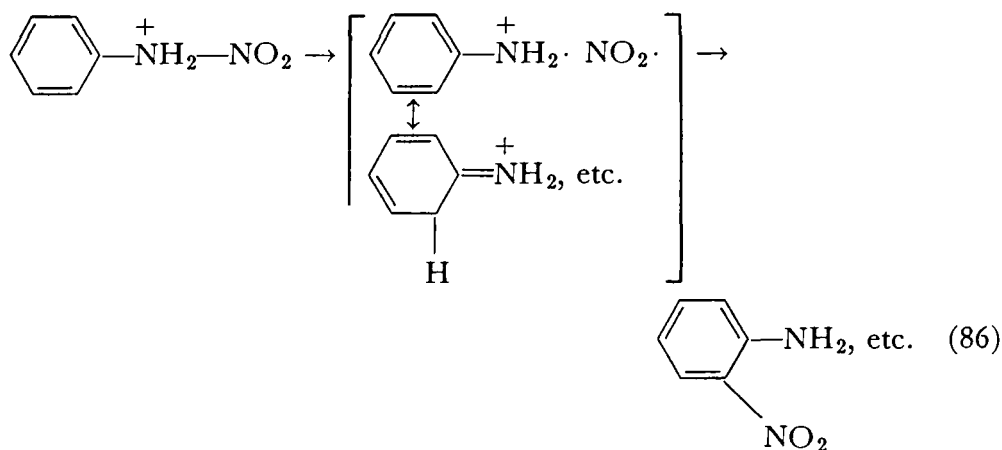


N-Nitroanilines are a special case; warm dilute acid causes their rearrangement to a mixture of *ortho*- and *para*-nitroanilines (Eq. 85).



Notwithstanding intensive investigation, this rearrangement still presents enigmatic aspects. The original assumption that the rearrangement was intramolecular was thought to have been confirmed by the demonstration that there is no isotope exchange with ambient nitric acid, but it was subsequently pointed out ¹⁶⁵ that such an experiment only had validity if it could be assumed that any intermolecular reaction must take place through heterolytic denitration to nitric acid (or nitronium ion). Indeed, the *ortho*/*para* isomer ratio in the products is distinctly different from that obtained by direct nitration of the corresponding aniline. A more acceptable criterion of intramolecularity would be the lack of isotope

exchange during the simultaneous rearrangement of two different N-nitroanilines of similar reactivity.¹⁶⁶ In one case (N-nitro-N-methylaniline and its *p*-fluoro derivative with nitro-¹⁵N), partial intermolecularity was revealed; in another (*p*-tolylnitramine and phenylnitramine nitro-¹⁵N), no cross-over could be detected. To account for these observations, it has been proposed¹⁶⁶ that the protonated nitramine undergoes homolytic fission to nitrogen dioxide and a cation radical; recombination to form the products may occur within the solvent cage (therefore intramolecularly) or after diffusion outside it (intermolecularly) (Eq. 86).

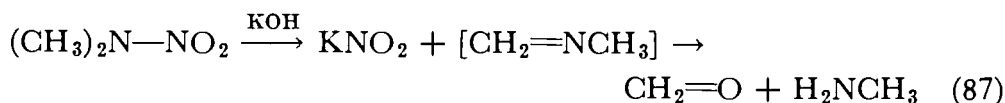


The foregoing rearrangement of arylnitramines is circumvented by treatment with sulfuric acid in an excess of phenol^{11, 167}; the parent amine is then produced, apparently in useful yields, for the method has been recommended for preparative purposes in special situations. Aliphatic nitramines are apparently not susceptible to this reaction. Under slightly different conditions (phenol and very dilute aqueous sulfuric acid), a variant of the Liebermann nitroso test is obtained.¹¹ The result with nitramines appears to differ from that with nitrites and nitrosamines in that the color that develops when the mixture is subsequently made basic differs from the typical blue color and is likely to be green; however, the essential similarity does not recommend the Liebermann test as a reliable method for distinguishing nitramines from nitrosamines.

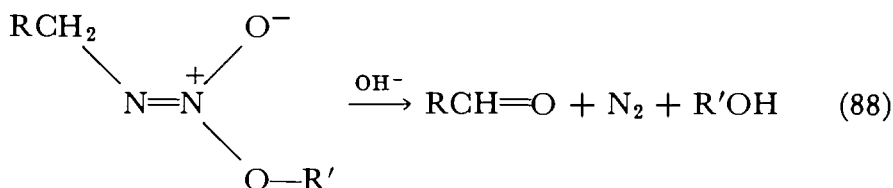
The large amount of research on the behavior of *gem*-dinitramines toward acid,^{20, 161, 168} mostly oriented toward the preparation of the explosive, RDX (cyclonite), will not be dealt with here.

BASE Primary nitramines form salts with bases and are thereafter relatively inert. Secondary nitramines are also fairly unreactive toward bases, but hot alkali slowly decomposes them by effecting elimination of nitrous acid to form an aldehyde or ketone and a primary amine^{16, 169} (Eq. 87). A related reaction is exhibited by the predominant geometrical

isomer (presumably the *trans*) of O,N-dialkylnitramines (Eq. 88); the

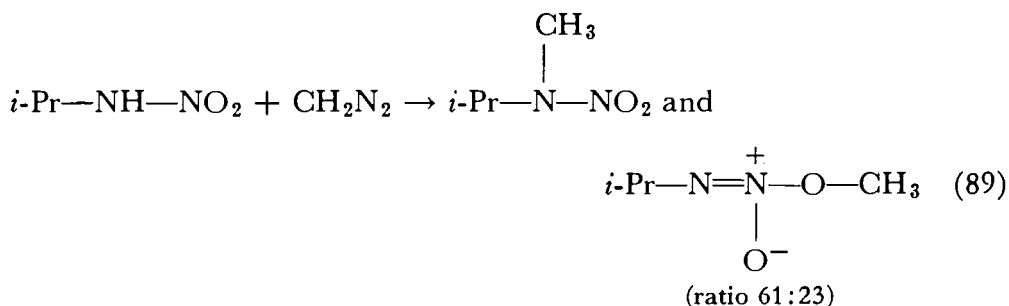


minor isomer apparently only loses the O-alkyl group, regenerating a

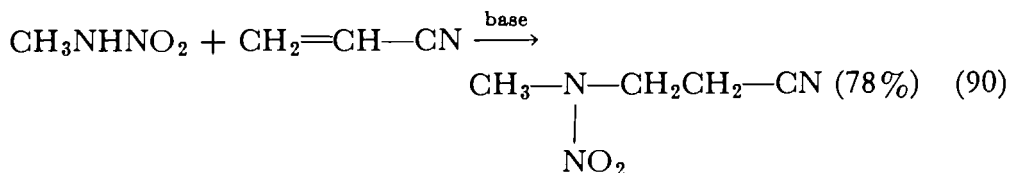


primary nitramine.¹⁵ N-Nitro amide derivatives of carbonic acid are easily cleaved by alkali, ammonia, or, in some cases, even by hot water to form nitramides^{11, 170} (apparently sometimes mistaken for hyponitrous acid). Nitramines have reportedly withstood boiling for an hour with alcoholic sodium ethoxide.¹⁷¹

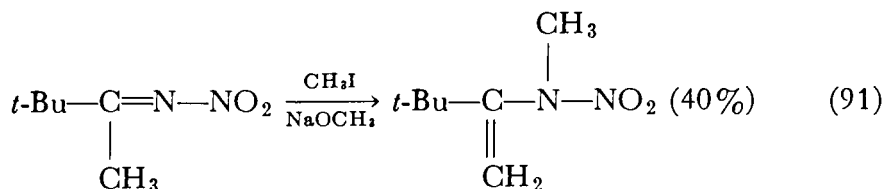
ALKYLATION Primary nitramines react with diazomethane to give a mixture of N-methyl and O-methyl isomers^{172a} (Eq. 89). The reaction



of potassium salts with small alkyl iodides gives mostly N,N-dialkylnitramine, but the proportion of the O,N-dialkyl isomer increases with the bulk of the alkyl groups; silver salts give almost entirely the N,O-dialkyl isomer regardless.¹⁷² This is typical behavior for an ambident anionic system and recalls the parallel difference in the alkylation of silver and potassium nitrites, which gives O-alkylation and N-alkylation, respectively. Michael-type alkylation with acrylonitrile, methyl vinyl ketone, etc., appears to take place entirely on nitrogen¹⁷³ (Eq. 90). N-Nitro-

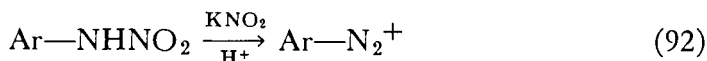


urethans are readily alkylated, apparently entirely on nitrogen, by diazoalkanes.¹⁷⁴ The salts of nitrimines, which are derived by removal of a proton from an α -carbon, are interestingly enough alkylated at the imine nitrogen by methyl iodide²¹ (Eq. 91).



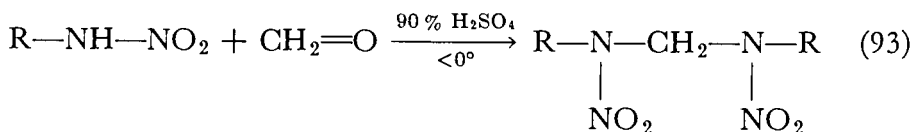
ACYLATION The reaction of salts of primary nitramines with acid chlorides has already been mentioned in connection with the thermal decomposition of N-nitro amides. In addition to the decomposition products of the presumed O-acyl nitramine (Eq. 78), small amounts of N-acyl compound (N-nitro amide) are sometimes obtained.^{11, 75} Methyl chloroformate appears to be unusual in giving substantial amounts of N-acyl product.

CHLORINATION AND NITROSATION Hypochlorites convert aryl nitramines to unstable oils that are apparently N-chloro derivatives; they rearrange spontaneously to their ring-chlorinated isomers.¹⁷⁵ Nitrous acid (or even potassium nitrite) reacts with primary nitramines to form diazonium salts or their decomposition products (Eq. 92); the reaction has been little studied with aliphatic examples,¹⁷⁶ but with aryl nitramines



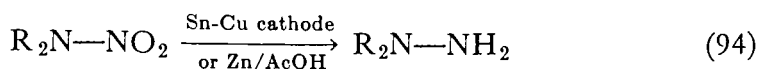
it appears to be general and clean.¹⁷⁷

CARBONYL COMPOUNDS Primary nitramines, like ordinary secondary amines, react with formaldehyde to form *gem*-diamine derivatives.¹⁷⁸ The conditions are considerably different, but the yields are moderate to good (Eq. 93). Primary nitramines may also play the role of the

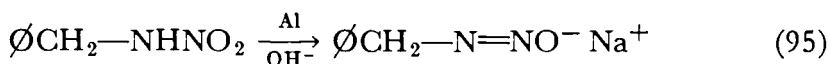


active-hydrogen compound in the Mannich reaction¹⁷⁹; the N-dialkylaminomethyl nitramines produced are unstable toward acid.

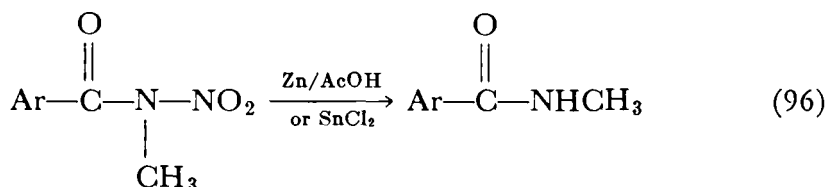
REDUCTION N-Nitro compounds may be reduced so as to give products belonging to one of three stages: nitrosamine, hydrazine, or amine. Electrolytic reduction has given good yields of hydrazines from nitramines^{11, 180} (Eq. 94). Zinc reduction usually produces significant quan-



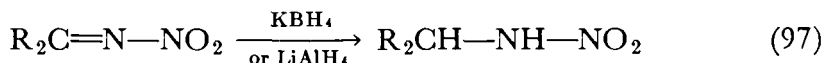
ties of amine as well,¹⁸¹ and yields are sometimes low. Aryl nitramines, on the other hand, are reduced to diazonium salts by zinc and acetic acid.¹⁸¹ In one instance, N-methyl-N-phenylnitramine, a nitrosamine has been isolated (yield *ca.* 25%) from cautious reduction with a very limited amount of zinc.^{181b} Aluminum and alkali^{14b, 182} or sodium amalgam¹⁸¹ produce nitrosamine salts (Eq. 95), which may decompose to diazoalkanes when the substituent is aliphatic; excess reducing agent eventually produces a hydrazine. Zinc and acetic acid, or stannous



chloride, generally denitrate N-nitro amides to amides (Eq. 96), but



nitrourethans can be reduced to hydrazides.^{145, 183} Nitrimines are reduced to imines (or the primary amines resulting from further reduction) by catalytic hydrogenation,¹⁸⁴ but potassium borohydride or lithium aluminum hydride reduces nitrimines to primary nitramines²¹ (Eq. 97),



an example of selectivity very similar to the reduction of nitro olefins to nitroalkanes by the same reagents.

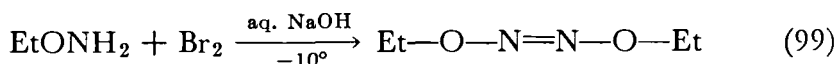
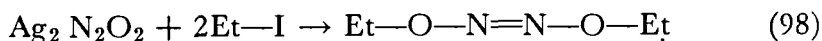
Primary and secondary nitramines and N-nitro amides give a characteristic color reaction when reduced by zinc in an acetic acid solution of an aromatic amine, usually β -naphthylamine (violet test).^{11, 85, 186} This reaction has come to be known as the Franchimont test for the N-nitro structure. Its mechanism is obscure; it is evidently not a case of diazotization by nitrous acid released by reduction of the nitramine to a nitrosamine, for nitrosamines themselves do not give the test, and a tertiary aromatic amine (dimethylaniline) may be used as the reagent in place of naphthylamine. O,N-Dialkylnitramines do not respond to the Franchimont test^{172b} and are thereby distinguished from their N,N-dialkylnitramine isomers.

OXIDATION Nitramines are not easily oxidized¹¹; witness their preparation by oxidation of nitrosamines. However, methylnitramine is reported to be destroyed by warming with potassium permanganate solution with evolution of nitrous oxide.¹⁸⁷

PREPARATIVE METHODS

A. Hyponitrites

The only method of demonstrated preparative value so far reported for hyponitrites is the alkylation of silver hyponitrite with alkyl halides,^{1, 2} although a patent claim exists for oxidation of alkoxyamines to hyponitrites¹⁸⁸ with a variety of oxidizing agents, including hypobromite, mercuric oxide, peroxides, etc. (Eqs. 98, 99).

**B. Nitrites**

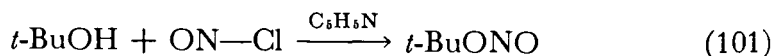
All preparative methods for alkyl nitrites involve interaction of an organic compound with nitrous acid or some simple derivative of it. The simplest method and the most widely used is the direct esterification of an alcohol with aqueous nitrous acid liberated from sodium nitrite by sulfuric acid, a reaction that proceeds at 0° without the necessity for special efforts to remove water. Preparations of methyl nitrite,¹⁸⁹ ethyl nitrite,¹⁹⁰ and butyl nitrite¹⁹¹ (Eq. 100) by this method are described in *Organic Syntheses*. The mechanism of the reaction, which has much in



common with the diazotization of amines, has been studied in somewhat less detail.^{192, 193} A potentially useful variant of this procedure is the treatment of a mixture of the alcohol and saturated aqueous sodium nitrite with aluminum sulfate; isoamyl nitrite, for example, is thus obtained in 91% yield.¹⁹⁴

The gaseous alkyl nitrites (methyl and ethyl) can also be generated with great simplicity by transesterification with a higher-boiling nitrite (amyl is commonly used); the gaseous nitrite is spontaneously evolved without a catalyst.^{70a} Thiolnitrites may be prepared analogously, using a mercaptan at -35°, except, of course, that the product is not evolved as a gas.⁵⁹

Nitrosyl chloride, used in the presence of pyridine, has been used to convert *tert*-butyl alcohol to its nitrite¹⁹⁵ (Eq. 101) and has also been



used to convert mercaptans to thiolnitrites.⁵⁹ A number of primary alkyl nitrites have been prepared from alcohols and nitrosyl fluoborate; yields were moderate.¹⁹⁶

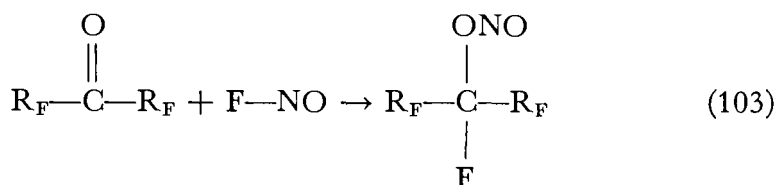
Alkyl halides can be converted to nitrites, along with variable amounts of the isomeric nitroalkane, by reaction with silver nitrite ¹⁹⁷ (Eq. 102). This reaction takes place with inversion of configuration at the site of



attachment.¹⁹⁸

Olefins do not add nitrous acid, but they can be converted to β -nitro nitrites (accompanied by β -nitro nitrate and the *vic*-dinitro analog) by addition of dinitrogen tetroxide to olefins.^{61, 199}

Some secondary perfluoroalkyl nitrites have been prepared by the addition of nitrosyl fluoride to perfluoro ketones ²⁰⁰ (Eq. 103), a reaction



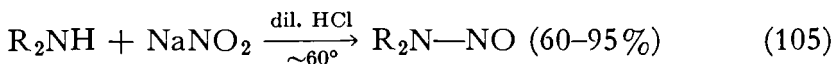
without analogy in nonfluoro chemistry.

Perfluoroacyl nitrites have been prepared by the reaction of perfluoro acid anhydrides with nitrous anhydride or nitrosyl chloride (Eq. 104),^{4, 201} and by the reaction of salts of perfluoro acids with nitrosyl chloride.²⁰²



C. *N*-Nitroso Compounds

Secondary nitrosamines are generally prepared by treatment of secondary amines with sodium nitrite and an excess of dilute acid, usually with moderate warming ^{84, 203, 204} (Eq. 105). Directions for dimethyl-

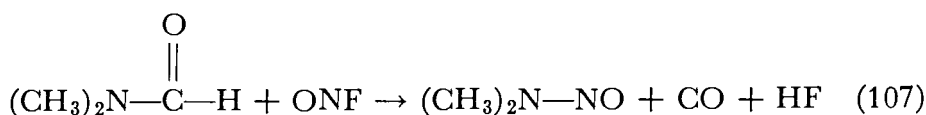


nitrosamine and *N*-nitroso-*N*-methylaniline are given in *Organic Syntheses*.^{205, 206} Tertiary amines can be converted to secondary nitrosamines by essentially the same method ²⁰⁷⁻²⁰⁹; for best results, a large excess of nitrite is used, the acidity is kept low, and temperatures of 60-90° are used (cf. Chapter 2). Only exceptionally do primary amines ⁷ give rise to primary nitrosamines on treatment with nitrous acid.

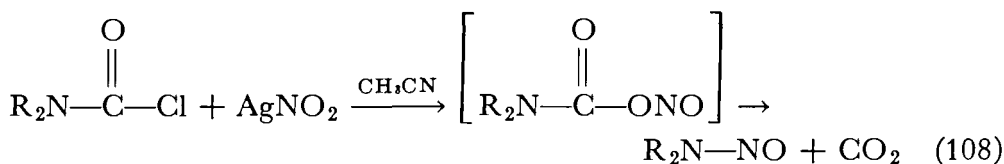
Nitrosation of secondary amines can be carried out with nitrosyl fluoborate,¹⁹⁶ but there seems to be no general advantage. Nitrosyl chloride is useful with primary amines, for it is active at the low temperatures required to stabilize the primary nitrosamines formed ⁶ (Eq. 106). *N*-Nitroso-3-nitrocarbazole has been used to prepare other secondary



nitrosamines by a nitroso-transfer reaction ³¹; yields are only moderate, but the method has the potential advantage of functioning in the absence of acid. Nitrosyl fluoride has been used to prepare nitrosamines by cleavage of dialkylformamides ²⁰⁰ (Eq. 107).

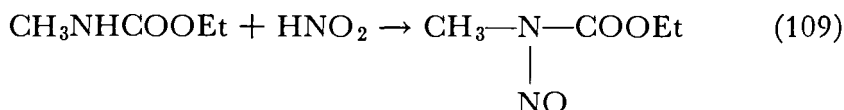


Two nonnitrosative reactions leading to nitrosamines are available, but only one of them, the reaction of carbamyl chlorides with silver nitrate, ²⁰ appears to be of preparative value (Eq. 108). The other method, reduc-

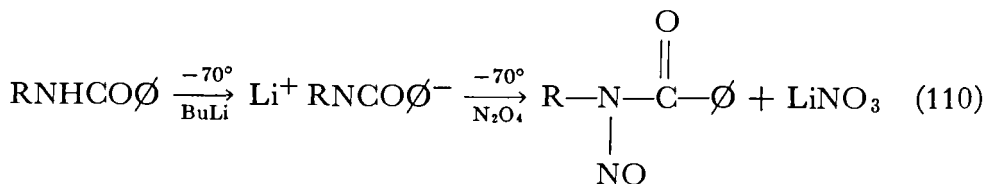


tion of nitramines, has been described earlier in this chapter.

N-Nitroso amides can be prepared in some instances by direct nitrosation of amides with nitrous acid ^{211, 212} (Eq. 109), but it is generally necessary to use a more powerful nitrosating agent, such as nitrous anhy-



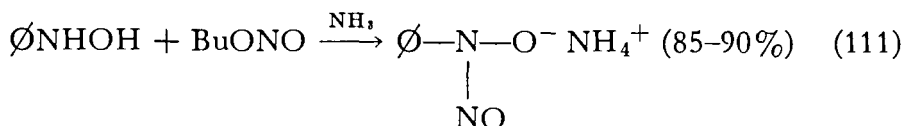
dride, nitrosyl chloride, ²¹³ or dinitrogen tetroxide for best results. ^{74a} Indeed, the last reagent, used in the presence of anhydrous sodium acetate at depressed temperatures, appears to provide the method of choice, for it reacts with secondary-alkyl as well as primary-alkyl amides, and when supplemented by conversion of the amide to its lithium derivative, converts even tertiary-alkyl amides to their N-nitroso derivatives ²¹⁴ (Eq. 110).



Nitrosimines, too, are prepared by nitrosating ketimines with dinitrogen tetroxide in the presence of sodium acetate. ¹⁰

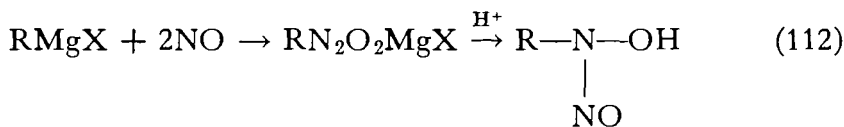
N-Nitrosohydrazines are generally prepared by direct nitrosation with aqueous nitrous acid. ^{13, 14b, 111-113} N-Nitrosohydroxylamines, on the other hand, are best prepared by alkaline nitrosation with alkyl ni-

trites ^{11, 18a, 126, 215} (Eq. 111), although nitrosation with nitrous acid in weakly acid solution is also satisfactory.^{106a, 217, 218} The required hydroxylamines are not always easily obtainable, wherefore it may sometimes



be of advantage to utilize the route through peroxide oxidation of N-nitroso anilides, which generally gives high yields.⁹⁶ Nitrobenzenes can in some cases ²¹⁹ be converted directly to salts of the corresponding nitrosohydroxylamine by treatment with sodium ethoxide and hydroxylamine or sources of nitroxyl, such as sodium nitrohydroxamate, $\text{Na}_2\text{N}_2\text{O}_3$. The oxidation of N-nitrosophenylhydrazine to N-nitrosophenylhydroxylamine by cupric salts has been mentioned earlier in this chapter.

An entirely different route to nitrosohydroxylamines makes use of the reaction of organometallic compounds with nitric oxide ^{107b, 220, 221} (Eq. 112). Both aromatic and aliphatic compounds can be made in this way



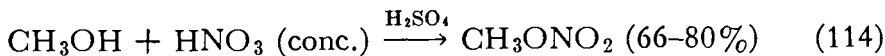
in moderate to good yields. It appears that any source of carbanions may take part in this reaction, for it is claimed that any compound with a hydrogen active enough to undergo nitrosation will give a nitrosohydroxylamine when treated with nitric oxide and a strong base; acetaldehyde and malonic esters are among the successful examples.^{13c, 222} Compounds with an active methylene group easily react twice, giving *gem*-nitrosohydroxylamines (Eq. 113).



D. Nitrates ⁴¹

The most widely used methods ¹³⁶ for the preparation of alkyl nitrates are direct esterification of the corresponding alcohol, or treatment of an alkyl halide with silver nitrate.

Esterification of alcohols with nitric acid is generally conducted in the cold, but sometimes up to 40°, using yellow fuming nitric acid (90–100%) alone or in acetic anhydride, ^{127, 223, 224} or a mixture of concentrated nitric and sulfuric acids ^{136, 225} (Eq. 114). There is real danger of such



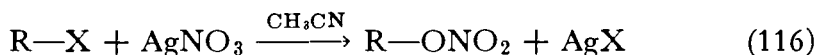
direct nitrations running out of control, even to the extent of explosion,

if proper precautions are not taken, especially with small or easily oxidized alcohols, and it is particularly important to pay careful attention to conditions in large-scale preparations.^{224, 226} The kinetics of nitration of alcohols are closely related to those for aromatic nitration, and it is apparent that in both cases the active agent is nitronium ion^{227, 228} (NO_2^+). Indeed, nitrate esters can be made readily by alcoholysis of nitronium fluoborate¹⁹⁶ (Eq. 115). Alcoholysis of acyl nitrates (e.g.,



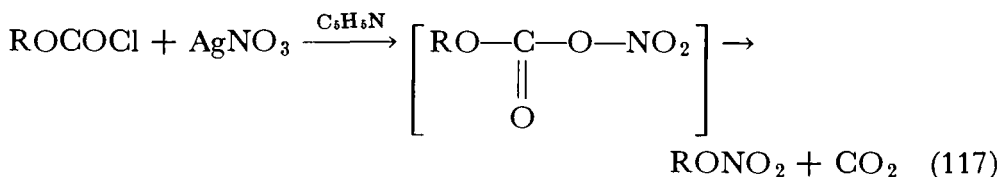
benzoyl nitrate) is also successful.²²⁹

The reaction of alkyl halides with silver nitrate⁴¹ may be conducted heterogeneously or in solution in acetonitrile²³⁰ (Eq. 116). Unless the



alkyl group is allylic, benzylic, or tertiary, the reaction is for practical purposes limited to bromides and iodides.

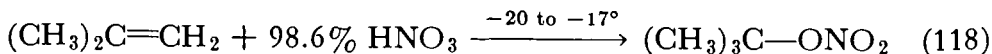
A newer preparative method that is quick and has the advantage of unusual mildness is the reaction of alkyl chloroformates with silver nitrate (Eq. 117); the intermediate nitric carboxylic anhydride decomposes



spontaneously at room temperature.²³¹

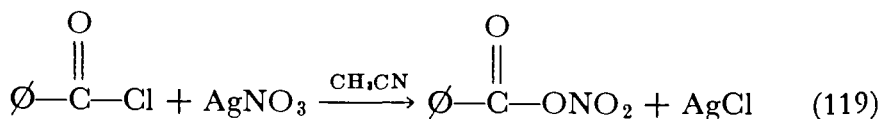
Oxidation of alkyl nitrites to nitrates, although accomplished successfully by ethyl hydroperoxide,⁶⁰ does not appear to have preparative use.

In favorable situations, nitric acid can be caused to add to olefins to give nitrates; this method has some value in the preparation of *tert*-butyl nitrate, for example²³² (Eq. 118).



β -Nitroalkyl nitrates can be prepared by the addition of dinitrogen tetroxide to olefins¹⁹⁹; β -nitroalkyl nitrites and vicinal dinitro compounds are formed as well and must be separated.

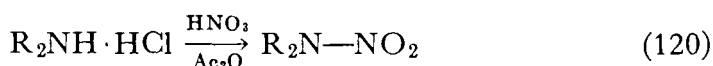
Acyl nitrates can be prepared by the reaction of acyl chlorides with silver nitrate¹⁴⁷ (Eq. 119) and by the reaction of anhydrides with absolute



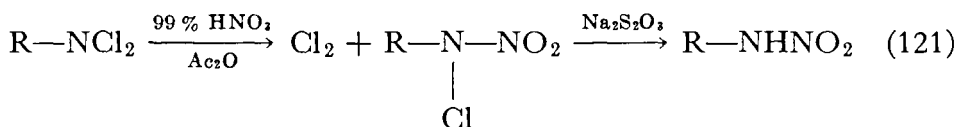
nitric acid.¹⁴⁶

E. Nitramines ^{11, 20, 233}

Direct nitration of amines with nitric acid is only exceptionally successful, owing to the fact that the strongly acid conditions required to generate the active nitrating species, nitronium ion,²³⁴ at the same time remove all but the most weakly basic amines as ammonium ion (some anilines with strongly deactivating substituents have been nitrated on the nitrogen, for example). As a consequence, various indirect means have been developed. The simplest of these is the use of chloride as a catalyst, which may be introduced as the amine hydrochloride or as zinc chloride. Nitration is carried out with fuming nitric acid in acetic anhydride ^{172b, 235} (Eq. 120). The function of the chloride is evidently to serve as a source

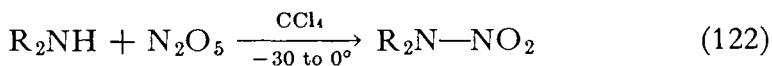


of chlorine (oxidation by nitric acid) to convert some amine to a chloramine, which, being much less basic, can react with nitric acid to form the nitramine and regenerate chlorine ²³⁶ (or Cl^+). Indeed, chloramines themselves are readily nitrated; N,N-dichloroamines can be used in the preparation of primary nitramines through the intermediacy of N-chloro-nitramines ^{172c} (Eq. 121). Ordinarily, acidic nitration of primary amines

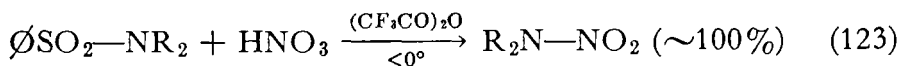


is not successful, apparently because nitramines are so easily decomposed by strong acid.

Direct nitration of secondary amines has been accomplished with nitrogen pentoxide in carbon tetrachloride solution in high yields (Eq. 122); this method gives but traces of primary nitramines, however.²³⁷



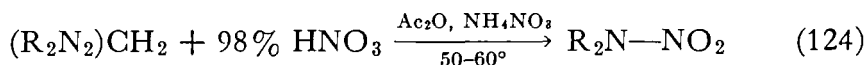
A widely used method to circumvent the hindering action of strong acid in tying up the amine as a salt is to use N,N-disubstituted amides; some acyl groups are readily removed by nitrolysis in the nitrating medium, thus giving rise directly to nitramines (Eq. 123).^{11, 180, 238} Acetamides and sulfonamides are most generally used, but formamides ^{239a}



and N,N-dialkyl ureas ^{239b,c} are also useful. The competing reaction of oxidative dealkylation to give a nitro amide is in some cases dominant, and with N,N-dialkylurethans is practically the sole reaction.¹¹ This

general method is in principle the same as the nitration of chloramines and is probably the principle behind the conversion of nitrosamines to nitramines by reaction with nitric acid ^{94b} (see "Reactions").

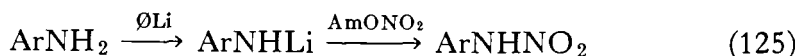
Secondary nitramines can in exceptional cases be made through cleavage of tertiary amines, mostly N,N-dialkyl anilines, under nitrating conditions, as in the preparation of tetryl (N,2,4,6-tetranitro-N-methylaniline) from dimethylaniline ²⁴⁰; a trace of nitrous acid is essential for this reaction. Of somewhat greater generality is the nitrative cleavage of tertiary *gem*-diamines, ²⁴¹ whose low inherent basicity renders them susceptible to nitration under strongly acidic conditions (Eq. 124); this reaction is the basis of the synthesis of RDX (trimethylenetrinitramine) by



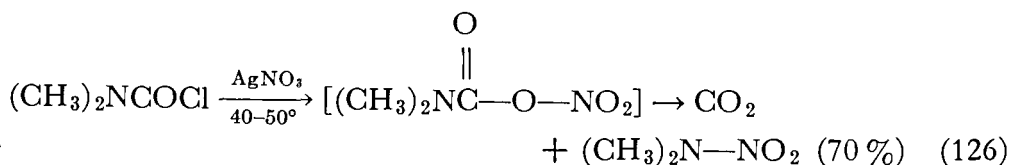
nitration of hexamethylenetetramine. ^{20, 242} It is important that the nitric acid be free of lower oxides in this case.

Primary nitramines are best made under alkaline conditions, so that the product is stabilized as a salt. Alkaline nitration with α -cyanoisopropyl nitrate is a good general method ²⁴³ (see also the discussion under "Reactions. D. Nitrates"); this reagent may also be used to nitrate secondary amines (N-nitromorpholine, for example, can be prepared in 57–64% yield ²²⁴). Before the introduction of α -cyanoisopropyl nitrate, primary nitramines were generally prepared by the alkaline hydrolysis of N-nitro urethans or ureas, ^{11, 160, 244} a method that still remains useful. The required N-alkyl-N-nitro compounds can be obtained by alkylation of nitrourethan ¹⁷⁴ (see "Reactions") or by nitration of an N-alkyl urethan or urea (see ahead).

Primary nitramines can be made by alkaline nitration with even ordinary alkyl nitrates, such as amyl, if the amine is first converted to its lithium derivative by treatment with butyl- or phenyllithium ²⁴⁵ (Eq. 125).



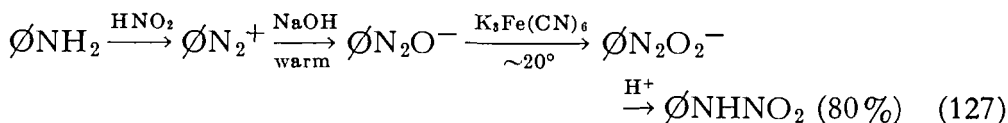
Nitramines can be made smoothly by the reaction of carbamyl chloride with silver nitrate ²¹⁰ (Eq. 126), a reaction that appears to be



in every way analogous to the preparation of nitrosamines from carbamyl chlorides.

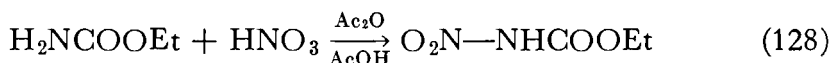
Oxidation of *anti*-diazotates is a general synthesis for primary nitramines. ^{14b, 90} It is a particularly valuable method for aryl nitramines ²⁴⁶

because of the easy availability of the diazotates from the corresponding aniline (Eq. 127); potassium ferricyanide appears to be the oxidizing agent

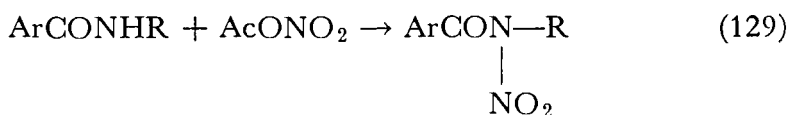


of choice. Secondary nitramines have been prepared by oxidation of secondary nitrosamines with peroxytrifluoroacetic acid (cf. "Reactions," C).^{94a}

N-Nitro amides are in general prepared by direct nitration in strongly acidic solution, using either yellow fuming nitric acid, "mixed acids," or acetyl nitrate. The nitration of unsubstituted amides is seldom successful except for urethan (Eq. 128)^{160, 247} and urea, however, and the reaction

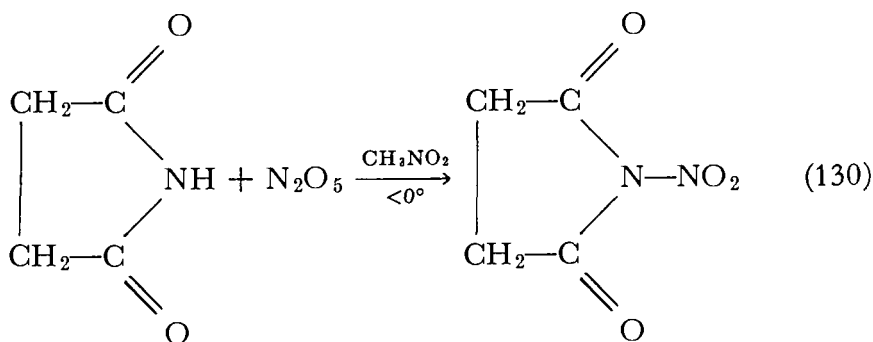


is otherwise ordinarily confined to the preparation of N-substituted-N-nitro amides^{11, 145, 244} (Eq. 129). Nitrourea^{248a} and nitroguanidine^{248b}

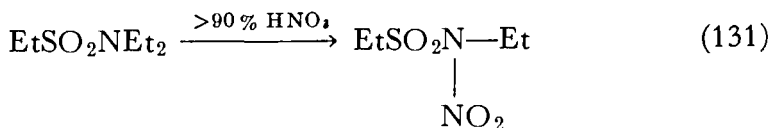


are customarily prepared by treating crystallized urea nitrate or guanidinium nitrate with concentrated sulfuric acid below room temperature.

Amides may also be nitrated with nitrogen pentoxide (used in chloroform or nitromethane)²⁴⁹; yields are generally above 90%, and even imides, which are otherwise nearly inert, can be nitrated (Eq. 130). N-Nitro amides have also been prepared by nitration of certain dialkyl



amides, particularly dialkylurethans, that do not readily undergo deacylative nitrolysis^{11, 250} (Eq. 131).



Oxidation of N-nitroso amides is not regarded as a synthetic method for N-nitro amides, although it has been used successfully in the preparation of nitroguanidine.⁹⁵

Nitrimines are generally prepared by the reaction of diazoalkanes with nitric oxide through azine N,N'-dioxide intermediates²⁵¹ (see Chapter 11) and by the reaction of dinitrogen tetroxide with oximes^{21, 171} (cf. Chapter 8). There appears to be only one reported case of the preparation of a nitrimine by reaction of nitramide with a carbonyl compound (furfural) (Eq. 132).²⁵²



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